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Bioactive factor delivery strategies from engineered polymer hydrogels for therapeutic medicine

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Abbreviations: GFs, growth factors; ALG, alginate; HA, hyaluronic acid; HEP, heparin; PEI, polyethyleneimine; PHEMA, poly(2-hydroxyethyl methacrylate); PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); DEX, dextran; PPO, poly(propylene oxide); PPG, poly(propylene glycol); (PNIPAm), poly(*N*-isopropylacrylamide); PEO-PPO-PEO, poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide); Pluronic®, same as PEO-PPO-PEO; HDI, hexamethylene diisocyanate; PCL, poly(ε-caprolactone); PLA, poly(lactic acid); ROP, ring opening polymerization $Sn(oct)_2$ stannous octoate; DEGDVE, di-(ethylene glycol) divinylether; *p*-TSA, *p*-toluenesulfonic anhydride; PGA, poly(glycolic acid); PHB, poly[(*R*)-3-hydroxybutyrate]; PLGA, poly(D,L-lactide-co-glycolide); MPEG, monomethoxy poly(ethylene glycol); DLLA, D,L-lactide; GA, glycolide; PVL, poly(δ-valerolactone); HB, (*R*)-3-hydroxybutyrate; EG, ethylene glycol; ATRP, atom transfer radical polymerization; MPC, poly(2-methacryloyloxyethyl phosphorylcholine); DEDBA, diethyl-*meso*-2,5-dibromoadipate; Cu(I)Br, copper(I) bromide; Me_4Cyclam, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclo-tetradecane; RAFT, reversible addition-fragmentation chain transfer; PNIPAm-PMMA, poly(NIPAm-*b*-methyl methacrylate); macro-CTA, macromer containing chain transfer agent; AIBN, 2,2′-azobis(2-methylpropionitrile); MCPDB, *S*-methoxycarbonylphenylmethyl dithiobenzoate; $AlCl_3$, aluminum chloride; IleOEt, L-isoleucine ethyl ester; LeuOEt, D,L-leucine ethyl ester; ValOEt, L-valine ethyl ester; PPF, poly(propylene fumarate); $ZnCl_2$, zinc chloride; PLLA, poly(L-lactide); PDLA, poly(D-lactide); $NaBH_3CN$, cyanoborohydride; PAA, poly(amidoamine); TMDP, 4,4-trimethylene dipiperidine; P(DEGMMA-*co*-MAA), poly(methoxydi(ethylene glycol) methacrylate-*co*-methacrylic acid); PAUU, poly(amino urea urethane); OSM, oligomer sulfamethazine; DMAP, 4-(dimethylamino)pyridine; DCC, *N*,*N*′-dicyclohexylcarbodiimide; PAE, poly(β-aminoester); BDA, 1,4-butandiol diacrylate; PAEU, poly(amino ester urethane); PANHS, palmitic acid *N*-hydroxysuccinimide; CD, cyclodextrins; HPMA, poly(*N*-(2-hydroxypropyl)methacrylamide); APMA, *N*-(3-aminopropyl)methacrylamide; PA, polyalanine; NCA, carboxy anhydrides; PLX, PPG-PEG-PPG bis(2-aminopropyl ether); AC, acryloyl chloride; Irgacure 651, 2,2-dimethoxy-2-phenylacetophenone; PEGDA, poly(ethylene glycol) diacrylate; PEGLADA, poly(ethylene glycol)-lactic acid-diacrylate; PHPMAlac, poly(*N*-(2-hydroxypropyl)methacrylamide lactate); Irgacure 2959, 4-(2-hydroxyethoxy)phenyl-(2-hydroxy-2-propyl)ketone; ALG-MA, methacrylated alginate; EDC, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; NHS, *N*-hydroxysuccinimide; AEMA, 2-aminoethyl methacrylate; CMC, carboxymethylcellulose; PEGDM, poly(ethylene glycol) dimethacrylate; NORB, 5-norbornene-2-carboxylic acid; NASI, *N*-acryloxysuccinimide; DTP, dithiobis(propanoicdihydrazide); DTT, dithiothreitol; DEX-SH, thiolated-dextran; DEX-VS, dextran-vinyl sulfone; MMP, matrix metalloproteinase; $NaIO_4(NH_4)_2S_2O_8$, sodium periodate ammonium persulfate; NaOCl, sodium hypochlorite; $NaBH_4$, sodium borohydride; DTB, dithiobis(butyric dihydrazide); SPDP, *N*-succinimidyl 3-(2-pyridyldithio)propionate; DEX-CHO, aldehyde-modified dextran; AAD, adipic acid dihydrazide; $Na_2B_4O_7$, sodium tetraborate; CMC-CHO, oxidized carboxymethylcellulose; CMDX-ADH, hydrazide-modified carboxymethyldextran; HA-CHO, oxidized hyaluronic acid; *S*-chitosan, *N*-succinyl-chitosan; HRP, horseradish peroxidase; TGase, transglutaminase; PVA, poly(vinyl alcohol); CDI, *N*,*N*′-carbonyldiimidazole; APS, ammonium persulfate; TEMED, *N*,*N*,*N*′,*N*′-tetramethylethylene diamine; P(PF-*co*-EG), poly(propylene fumarate-co-ethylene glycol); *o*-NBE, *ortho*-nitrobenzylether; BGP, β-glycerophosphate disodium salt; G, α-guluronic acid; $CaSO_4$, calcium sulfate; $CaCl_2$, calcium chloride; $CaCO_3$, calcium carbonate; semi-IPN, semi-interpenetrating network; GAR IgG, goat anti-rabbit immunoglobulin G; AAm, acrylamide; MBA, *N*,*N*′-methylene bisacrylamide; AAc, acrylic acid; AFP, anti-AFP anti-α-fetoprotein antibody; PPxY, proline-rich peptide; DDD, docking and dimerization domain; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; AD, anchoring domain; AKAP, A-kinase anchoring protein; DMT, dexamethasone; SD, Sprague Dawley; 5-FU, 5-fluorouracyl; Ig, bovine γ-globulin; BSA, bovine serum albumin; siRNA, short interfering ribonucleic acid; GLP-1, glucagon-like peptide-1; DOX, doxorubicin; PAC, paclitaxel; AmB, amphotericin B; VEGF, vascular endothelial growth factor; GAG, glycosaminoglycan; β-NGF, β-nerve growth factor; PDGF-BB, platelet derived growth factor-BB; GDNF, glial-derived neurotrophic factor; bFGF, basic fibroblast growth factor; TGF-β1, transforming growth factor-β1; BMP-2, bone morphogenetic protein-2; SPR, surface plasmon resonance; SELEX, systematic evolution of ligands by exponential enrichment; PCR, polymerase chain reaction; ICG, indocyanine green; GOD, glucose oxidase; Con A, concanavalin A; PBA, phenylboronic acid; PNIPMAAm, poly(*N*-isopropylmethacrylamide); CaM, calmodulin; TFP, trifluoperazine; LCST, lower critical solution temperature; AMF, alternating magnetic field; XG, xanthan gum; UCNP, upconverting nanoparticle.

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ABSTRACT

Polymer hydrogels have been widely explored as therapeutic delivery matrices because of their ability to present sustained, localized and controlled release of bioactive factors. Bioactive factor delivery from injectable biopolymer hydrogels provides a versatile approach to treat a wide variety of diseases, to direct cell function and to enhance tissue regeneration. The innovative development and modification of both natural- (e.g., alginate (ALG), chitosan, hyaluronic acid (HA), gelatin, heparin (HEP), etc.) and synthetic- (e.g., polyesters, polyethyleneimine (PEI), etc.) based polymers has resulted in a variety of approaches to design drug delivery hydrogel systems from which loaded therapeutics are released. This review presents the state-of-the-art in a wide range of hydrogels that are formed though self-assembly of polymers and peptides, chemical crosslinking, ionic crosslinking and biomolecule recognition. Hydrogel design for bioactive factor delivery is the focus of the first section. The second section then thoroughly discusses release strategies of payloads from hydrogels for therapeutic medicine, such as physical incorporation, covalent tethering, affinity interactions, on demand release and/or use of hybrid polymer scaffolds, with an emphasis on the last 5 years.

Contents

1. Introduction

Bioactive factor delivery is a promising strategy to treat a variety of human diseases and enhance tissue regeneration, and this field has progressed significantly with the accelerated development of novel biomaterials and technologies [1–6]. The term 'bioactive factor' refers to small-molecule drugs like anticancer drugs [7,8], genetic agents [9–11] and proteins such as growth factors (GFs) [2,12], which have been used to treat human diseases, guide and direct cell functions and/or enhance tissue regeneration. Hydrogels, highly-hydrated three-dimensional networks of crosslinked hydrophilic polymer, hold great potential in pharmaceutical and biomedical applications [4,13–18]. They are of great interest due to their ability to locally deliver entrapped therapeutics at the sites of interest in vivo in a spatiotemporally controlled and sustained fashion.

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