



Contents lists available at ScienceDirect

Progress in Polymer Science

journal homepage: www.elsevier.com/locate/ppolysci



Polysarcosine-containing copolymers: Synthesis, characterization, self-assembly, and applications

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ARTICLE INFO

Article history:

Received 12 June 2017
Received in revised form
30 November 2017
Accepted 21 January 2018
Available online xxx

Keywords:

Polysarcosine
Poly-*N*-methylglycine
Polypeptides
Polypeptoids
Self-assembly
Biomaterials
Biopolymers

ABSTRACT

Although the first polysarcosine (pSar) synthesis by Wesseley *et al.* was reported almost a century ago, it was only recently that pSar gained broader attention and is considered a potential alternative of poly(ethylene glycol) (PEG). In contrast to polyethers, such as PEG, pSar is a polypeptoid based on the amino acid sarcosine, i.e. *N*-methylated glycine. As a polymer, pSar combines PEG-like properties, e.g., excellent solubility in water, protein resistance, low cellular toxicity and a non-immunogenic character, while being based on endogenous material. Sarcosine can be obtained in a simple one-step reaction of bromoacetic acid and methylamine, easily transferred into the sarcosine *N*-(thio)carboxyanhydride and polymerized under living condition. This review provides a first comprehensive overview on pSar-containing block copolymers, which comprises of copolymers with polyesters, polyethers, polypeptides, polypeptoids, polyacrylates, others, as well as graft copolymers. The synthesis, characteristics and application of such polymers will be presented and discussed in detail. Finally, solution self-assembly and applications of pSar-containing block copolymers are reviewed underlining the enormous potential of this recently rediscovered polypeptoid material.

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Abbreviations: AA, amino acid; ABC, accelerated blood clearance; Aib, 2-aminoisobutyric acid; AIBN, azobisisobutyronitrile; Ala, alanine; AMM, activated monomer mechanism; CAC, critical aggregate concentration; Cbz, benzyloxycarbonyl; CD, circular dichroism; CL, caprolactone; CuAAC, copper(I)-catalyzed azide-alkyne cycloaddition; DCC, dicyclohexyl carbodiimide; DFT, density functional theory; D_h , hydrodynamic diameter; DHBC, double hydrophilic block copolymer; DLS, dynamic light scattering; DMAc, dimethylacetamide; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DP, degree of polymerization; DSC, differential scanning calorimetry; \bar{D} , dispersity; EPR, enhanced permeability and retention; FACS, fluorescence activated cell sorter; FCS, fluorescence correlation spectroscopy; FTIR, fourier transform infrared spectroscopy; GC-MS, gas chromatography–mass spectroscopy; Gly, glycine; GSH, glutathione; HATU, 1- [bis(dimethylamino)methylene]-1H-1,2,3-triazolo [4,5-b]pyridinium 3-oxid hexafluoro phosphate; HPLC, high-performance liquid chromatography; His, histidine; LCST, lower critical solution temperature; Leu, leucine; Lys(TFA), N_ϵ -trifluoroacetyl-L-lysine; MALDI-ToF-MS, matrix assisted laser desorption ionization time of flight mass spectroscopy; MMA, methylmethacrylate; M_n , number average molecular weight; M_w , weight average molecular weight; NAG, *N*-allyl glycine; NAM, normal amine mechanism; NBG, *N*-*n*-butyl glycine; NBnG, *N*-benzyl glycine; NCA, *N*-carboxyanhydride; NCL, native chemical ligation; NDG, *N*-*n*-decyl glycine; NEG, *N*-ethyl glycine; NPhG, *N*-phenethyl glycine; NHC, *N*-heterocyclic carbene; NIBG, *N*-isobutyl glycine; NMP, *N*-methyl-2-pyrrolidone; NNCA, *N*-substituted *N*-carboxy anhydride; NOG, *N*-*n*-octyl glycine; NPeG, *N* glycine; NPG, *N*-*n*-propyl-*n*-propyl glycine; NPhG, *N*-phenyl glycine; NTA, *N*-thiocarboxyanhydride; pAla, polyalanine; PAMAM, poly(amido amine); PB, polybutadiene; PDLA, poly(D-lactic acid); PDLLA, poly(D,L-lactic acid); PEG, polyethylene glycol; Phe, Phenylalanine; pEtOx, poly(2-ethyl-2-oxazoline); pLys, polylysine; PLLA, poly(L-lactic acid); PMMA, poly(methyl methacrylate); PMOXA, poly(2-methyl-2-oxazoline); PS, polystyrene; pSar, polysarcosine; PTMI, poly(trimethyleneimine); PVA, Poly(vinyl alcohol); ROP, ring opening polymerization; RT, room temperature; S, styrene; Sar, sarcosine; SEC, size exclusion chromatography; SPAAC, strain promoted alkyne-azide cycloaddition; SPPS, solid phase peptide synthesis; TEM, transmission electron microscopy; WAXS, wide angle X-ray scattering; XPS, X-ray photoelectron spectroscopy.

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<https://doi.org/10.1016/j.progpolymsci.2018.01.002>
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Please cite this article in press as: Birke A, et al. Polysarcosine-containing copolymers: Synthesis, characterization, self-assembly, and applications. Prog Polym Sci (2018), <https://doi.org/10.1016/j.progpolymsci.2018.01.002>

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