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Polymer–drug conjugation, recent achievements and general strategies

G. Pasut, F.M. Veronese*

Department of Pharmaceutical Sciences, University of Padua, Via F. Marzolo 5, 35131-Padova, Italy

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Abstract

The field of drug delivery is fast expanding and its potentials have already been proved by the many products in the market. Among all approaches, polymer conjugation is a well known and widely exploited technique useful to improve therapeutic properties of peptides, proteins, small molecules or oligonucleotides. Polymer-conjugated drugs generally exhibit prolonged half-life, higher stability, water solubility, lower immunogenicity and antigenicity and often also specific targeting to tissues or cells. This technology, exploited for the first time in the fifties and sixties, received a great development both for the introduction and study of new and different polymers and for the progresses in the chemical strategies of coupling. Polymer–drug conjugates are already in the market for the treatment of different diseases, demonstrating the potentials of the technology. Furthermore, new polymers, in addition to the most known *N*-(2-hydroxypropyl)methacrylamide copolymer (HPMA), polyglutamic acid (PGA) and poly(ethylene glycol) (PEG), are continuously investigated and proposed. The review will discuss the most recent achievements in polymer conjugation with special emphasis on PEG application strategies and approved products.

Keywords: Polymer conjugation; Drug-delivery; PEG; PEGylation; Polymer therapeutics

Abbreviations: Å, Amstrong; AL–PEG, PEG aldehyde; BTC–PEG, PEG benzotriazolyl carbonate; CDI–PEG, PEG carbonylimidazole; CT-2103, PGA–paclitaxel conjugate; Da, Dalton; EGF, epidermal growth factor; EPR, enhanced permeability and retention; FDA, Food and Drug Administration; G-CSF, granulocyte colony stimulating factor; HCV, extrahepatic hepatitis C virus; hGH, human growth factor; HPMA, *N*-(2-hydroxypropyl)methacrylamide copolymer; IA–PEG, PEG–iodoacetamide; IFN, interferons; IL2, interleukine-2; IV, intravenous; kDa, kilo Dalton; MAL–PEG, PEG–maleimide; mPEG, monomethoxy-poly(ethylene glycol); MW, molecular weight; NCS, neocarcinostatin; NSCLC, non-small cell lung cancer; NHS, *N*-hydroxysuccinimide; OPSS–PEG, PEG–orthopyridyl-disulfide; PAcM, poly(acroloylmorpholine); PEG, poly(ethylene glycol); PEI, poly(ethyleneimine); PGA, polyglutamic acid; PHEG, poly((*N*-hydroxyethyl)-L-glutamine); PK1, HPMA–(Gly–Phe–Leu–Gly–doxorubicin)$_n$ conjugate; PK2, (*N*-acylated galactosamine)$_m$–HPMA–(Gly–Phe–Leu–Gly–doxorubicin)$_n$ conjugate; p*K*a, −log(dissociation constant); pNPC–PEG, PEG *p*-nitrophenyl carbonate; PVA, polyvinylalcohol; PVP, poly(vinylpyrrolidone); SC–PEG, PEG succinimidyl carbonate; SMA, poly(styrene-*co*-maleic acid/anhydride); SS–PEG, PEG succinimidyl succinate; TCP–PEG, PEG trichlorophenyl carbonate; TGase, transglutaminase; VS–PEG, PEG–vinylsulfone; wt%, weight percent

*Corresponding author. Tel.: +39 049 8275694; fax: +39 049 8275633.
E-mail addresses: gianfranco.pasut@unipd.it (G. Pasut), francesco.veronese@unipd.it (F.M. Veronese).

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Contents

1. Introduction

Biotech-derived drugs are increasingly used in the clinical practice and represent today an important share of the research and development budget of biopharmaceutical companies. Nowadays, thanks to the development of pharmaceutical biotechnologies, proteins and peptides are becoming potent and specific therapeutic agents, useful as replacement therapy or as inhibitors or regulators of the immune system for the treatment of important multifactorial diseases. However, these products still possess many intrinsic limitations to large-scale applications, such as low stability *in vivo*, short half-life and immunogenicity. The innovation in the design and production of biotech drugs, by recombinant DNA techniques, has been paralleled by important discoveries and improvements in the field of drug delivery, necessary to extend the half-life of these fragile products and to avoid the rapid clearance observed after their systemic administration. Different drug delivery systems have been developed in the last few years to improve the pharmacokinetic and pharmacodynamic profile of such compounds [1]. These approaches are based on the preparation of more favorable genetic variants or on tailor-made formulations of the drug, as liposomal preparations, controlled release systems, covalent modifications of the drug by low molecular weight reagent or by polymer conjugation. The last one is a fast growing technique that already produced several molecules available in the market [2], as shown in Table 1. The rationale for polymer conjugation is the possibility to prolong the plasma half-life of therapeutically active agents by increasing their hydrodynamic volume and hence decreasing their excretion rate. Furthermore, polymer chains can prevent the approach of antibodies, proteolytic enzymes or cells on conjugated molecules, an effect obtained by the steric hindrance of polymer strands.

Immunogenicity is likely to be one of the most serious problems, especially when dealing with heterologous proteins that commonly cause adverse response when recognized as non-self by the body immune system. This problem was addressed also in the first two papers of protein polymer conjugation highlighting, as an important result, the immunogenicity reduction of bovine albumin and catalase after PEG coupling [3,4]. The prevention of immunogenicity can be attributed to the shielding effect of polymeric chains surrounding the protein. This steric hindrance prevents interaction of antibodies or degrading enzymes with the protein (Fig. 1). In general, the conjugation of hydrophilic polymers deeply changes the behavior of the parent (free) compound both *in vitro* and *in vivo*. This change happens with both proteins and low molecular weight agents. Some advantages are (i) increased water solubility (important for very low soluble molecules as taxol, camptothecin or platinate derivatives); (ii) enhanced bioavailability and prolonged plasma half-life due to the increased