

Recent Applications of Polyethylene Glycols (PEGs) and PEG Derivatives

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Abstract

Numerous applications of polyethylene glycol derived polymers (PEGs) have been reported in the scientific literature for many years. With increasing experience and comfort by regulatory authorities, worldwide, in the utilization of these materials in drug and medical device applications, their use in a variety of research and development areas is expanding. This review will focus on just the range of applications of PEGs published in the first half of 2014 in the medical device, drug development, and diagnostics areas, including drug delivery, wound healing, cell culture models, and tissue regeneration.

Keywords: Polyethylene glycols; Drug development; Drug-release

Introduction

Polyethylene glycols (PEGs) are hydrophilic oligomers or polymers synthesized from ethylene oxide, consisting of a repeating unit of $-(O-CH_2-CH_2-O)-$. PEGs are synthesized in a wide range of molecular weights, referred to as "monodispersed", when there is a defined PEG chain size and molecular weight, or more commonly as "polydispersed" polymers, when there is a Gaussian distribution of chain lengths and molecular weights. The ability to attach a variety of reactive functional groups to the terminal sites of PEG polymers has greatly expanded their benefits. Hetero- and homo-bifunctional PEG derivatives are especially suitable as cross-linking agents or spacers between two chemical entities [1-3], whereas mono-functional PEGs prevent bridging reactions which may otherwise affect the PEGylation of certain compounds with bifunctional PEGs [4-7]. The sterically bulky structure of branched PEGs consisting of linear methoxy PEG chains attached to a central core, i.e., Y-shaped branched PEG derivatives, facilitates the single point attachment to targets [8,9] via a single reactive group. Multi-arm PEG derivatives (Figure 1) prepared by ethoxylation of different cores such as pentaerythritol, hexaglycerol, or tripentaerythritol, and incorporation of reactive moieties, are cross-linked easily into three-dimensional hydrogel materials [10-14] (Figures 1a-1c).

The process of PEGylation, the covalent grafting of a PEG derivative onto molecules, improves the water solubility and biocompatibility, especially useful for drug development [15]. PEGylated products require extensive characterization with complex analytical techniques [16-18] to ensure regulatory compliance for medical applications. Bifunctional PEG derivatives are used frequently for the PEGylation of peptides [19-21], proteins [22,23], small molecules like folate, mannose, pro-drugs [3,24], oligonucleotides [25], cells [26], nanoparticles and virus particles [23,27-32], and surfaces [33-37]. Multi-arm PEG derivatives are mostly employed in the formation of hydrogels [14,19,38-56] for controlled release of therapeutics; for use in medical devices; regenerative medicine; and in various other applications, including cell culture, wound sealing, and wound healing. Significant advances were made in 2014 by the scientific community in the research and development of novel applications for PEGs. Table 1 summarizes select novel applications of PEGs described in scientific publications in the first half of 2014, while the remainder of the publication highlights just those 2014 PEG applications related to the medical field.

Applications of Polyethylene Glycols for Cancer Drug Delivery and Targeted Diagnostics

R&D efforts on novel applications for PEG derivatives, published in the first half of 2014, focus in majority on drug delivery and targeted diagnostics, either via direct PEGylation of therapeutics [2,3,21,62-65]; or via PEG-containing vehicles, such as nanoparticles [64,65], liposomes [59], dendrimers [32,60], or micelles [57,58,61]. Important parameters that influence the bioactivity of the PEGylated drugs include the length of the PEG chain, the PEGylation site, the linker chemistry, and the temperature selected for the PEGylation reaction. For example, heat treatment was shown to improve the bioactivity of C-terminally PEGylated staphylokinases, whereas an amyli linker for a 20 kDa PEG increased significantly the bioactivity of staphylokinases [62]. The PEGylation of proteins is greatly influenced by the solvent

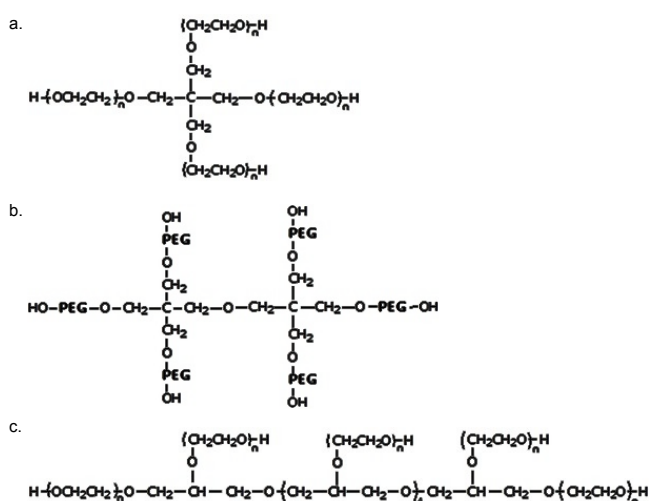


Figure 1: Representative illustrations of molecular structures for multiarm undervivatized polyethylene glycols

a. Molecular structure of an undervivatized 4arm polyethylene glycol

b. Molecular structure of an undervivatized 6arm polyethylene glycol polymer. In this particular structure, "PEG" stands for $-(CH_2CH_2O)_n-$

c. Molecular structure of an undervivatized 8arm polyethylene glycol polymer

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Polyethylene Glycol (PEG) Compound	PEG Applications	Reference
Biotin PEG SGA Ester, MW 3500	Cell PEGylation	[26]
Methoxy PEG Amine, HCl Salt, MW 2000	Diagnostics	[57]
4arm PEG Succinimidyl Carboxymethyl Ester, MW 40000	Drug delivery	[24]
Maleimide PEG Amine, MW 3500	Drug delivery	[2]
Maleimide PEG Hydroxyl, MW 3500	Drug delivery	[58]
Maleimide PEG NHS Ester MW 1000	Drug delivery	[59]
Maleimide PEG NHS Ester, MW 2000	Drug delivery	[21]
Maleimide PEG NHS Ester, MW 3500	Drug delivery	[59]
Maleimide PEG NHS Ester, MW 5000	Drug delivery	[60]
Methoxy PEG Amine, MW 12kDa	Drug delivery	[61]
Methoxy PEG Amine, MW 20kDa	Drug delivery	[62]
Methoxy PEG Carboxyl MW 3500	Drug delivery	[32]
Methoxy PEG Carboxyl, MW 1000	Drug delivery	[63]
Methoxy PEG NHS Ester, MW 5000	Drug delivery	[60]
Methoxy PEG Propionaldehyde MW 5000, MW 20kDa	Drug delivery	[62]
PEG Maleimide, MW 10000	Drug delivery	[22]
PEG NHS Ester MW 5000	Drug delivery	[59]
PEG Succinimidyl Carbonate, MW 10000	Drug delivery	[22]
PEG Thiol, MW 5000	Drug delivery	[59]
Amine PEG Carboxyl, HCl Salt, MW 5000	Drug delivery, Diagnostics	[3]
t-Boc Amine PEG Amine, HCl Salt, MW 5000	Drug delivery, Diagnostics	[3]
Amine PEG Carboxyl MW 3500	Drug delivery, Nanoparticle PEGylation	[64]
Methoxy PEG Amine MW 3500	Drug delivery, Nanoparticle PEGylation	[64]
4arm PEG Succinimidyl Carboxymethyl Ester, MW 10000	Hydrogel	[55]
4arm PEG Amine, MW 20kDa	Hydrogel	[14], [50], [53]
4arm PEG Thiol MW 10kDa	Hydrogel	[41]
4arm Polyethylene Glycol MW 10kDa	Hydrogel	[41]
4arm Polyethylene Glycol MW 20kDa	Hydrogel	[14], [43],[40], [45], [46], [50]
4arm Polyethylene Glycol MW 40kDa	Hydrogel	[46]
4arm Polyethylene Glycol, MW 5000	Hydrogel	[56]
8arm PEG Amine (tripentaerythritol), HCl Salt, MW 40000	Hydrogel	[39]
8arm PEG Amine HCl Salt MW 10kDa	Hydrogel	[47]
8arm PEG Thiol (hexaglycerol), MW 10000	Hydrogel	[44]
8arm Polyethylene Glycol (hexaglycerol), MW 10000	Hydrogel	[44], [53]
8arm Polyethylene Glycol (hexaglycerol), MW 15000	Hydrogel	[49]
8arm Polyethylene Glycol (hexaglycerol), MW 20000, MW 40000	Hydrogel	[38]
Acrylate PEG NHS Ester MW 3500	Hydrogel	[42], [48]
Methoxy PEG Amine, MW 2000	Hydrogel	[54]
6arm PEG Amine MW 10kDa	Nanoparticle PEGylation	[29]
Methoxy PEG Amine, MW 10000	Nanoparticle PEGylation	[65]
PEG Amine, MW 2000	Nanoparticle PEGylation	[29]
PEG NHS Ester MW 10kDa, MW 20kDa, MW 40kDa	Nanoparticle PEGylation	[27]
Thiol PEG Amine, MW 5000	Nanoparticle PEGylation	[28]
Methoxy PEG Amine, MW 5000	Nanoparticle PEGylation, Drug delivery	[30], [62]
Methoxy Polyethylene Glycol, MW 5000	Nanoparticle PEGylation, Drug delivery	[30]
8arm Polyethylene Glycol (tripentaerythritol), MW 20000	Peptide PEGylation	[19]
Methoxy PEG Amine HCl Salt MW 5000	Peptide PEGylation	[20]
Biotin PEG NHS Ester	Protein PEGylation	[35]
Methoxy PEG NHS Ester	Protein PEGylation	[35]
Thiol PEG Carboxyl, MW 5000	Protein PEGylation, Nanoparticle PEGylation	[23]
PEG Amine, HCl Salt, MW 20000	Surface modification	[33]
PLL20k-G35-PEG2k	Surface modification	[34,36,37]

Table 1: Select PEG compounds and their applications, cited in the first half of 2014.

used during the conjugation to the PEG. Peng et al. [22] discovered that organic solvents such as DMSO increase the degree of PEGylation, minimize the PEG hydrolysis, and decrease the PEGylation time for hydrophobic proteins such as G-CSF, compared to PEGylation in water phase. Selecting an organic solvent for hydrophobic proteins has the potential to reduce the cost of the reagents and the reaction times, parameters important for PEGylation processes on an industrial scale.

Among the many improvements brought to therapeutics by PEGylation are the increased water solubility, improved stability, controlled release, extended drug half-life, and an enhanced PK/PD (pharmacokinetic/pharmacodynamic) profile. PEGylation of therapeutic proteins occurs mainly on the N-terminal group, carbohydrates, sulfhydryl, and the aminoacids Thr, Cys, Asp, Glu Lys, His, Arg, Tyr, and Ser. In the course of the PEGylation of small

molecule drugs, a multi-arm polyethylene glycol will bond multiple drug molecules, ensuring a high drug load and an enhanced drug-release function [15]. As an example, increasing the molecular weight of the iRGD peptide by PEGylation prolonged the macromolecular extravasation and the overall drug penetration into tumors, and improved the pharmacokinetic profile of iRGD as compared to the unmodified peptide [21].

PEG-containing vehicles for drug delivery such as liposomes [59], dendrimers [60], nanoparticles [64,65], or micelles [57,58,61] are valid alternatives to direct PEGylation of drugs. Mei et al. [59] developed a multistage liposome drug delivery system co-modified with RGD, TAT, a specific ligand and a penetrating peptide, containing a cleavable PEG that increased the stability and circulation time of the liposomes. Liposomes undergo passive extravasation to tumor tissues, where the dual ligands become exposed through controlled exogenous administration of reducing L-cysteine. Subsequently, RGD recognize integrins, commonly overexpressed on malignant tumors, and mediate the internalization in a synergistic effect with TAT, penetrating deep into avascular tumor spheroids. Another type of PEG containing vehicle, a multifunctional dendrimeric carrier was developed by Kong et al. [60] for targeted delivery of the hydrophobic anticancer drug 10-hydroxycamptothecin (10-HCPT). The dendrimers consisted of integrated hydrophobic C12 alkyl chains with polyethylene glycol chains, and c(RGDfK) ligands on the surface. The dendrimer-10-HCPT drug complex exhibited higher drug loading and stability, and increased water solubility when compared to free 10-HCPT drug. The dendrimer-drug complex showed a higher cytotoxicity towards 22RV1 cells that overexpress integrin $\alpha v \beta 3$, and a lower cytotoxicity against MCF-7 cells with lower levels of integrin $\alpha v \beta 3$, following selective internalization of the complex into carcinoma cells via integrin receptor mediated endocytosis.

Drug delivery via PEG-modified nanoparticles is described in several 2014 publications. Super paramagnetic iron oxide nanoparticles containing a self-assembled copolymer of reducible polyamidoamine (rPAA) with polyethylene glycol/dodecyl amine on the surface, were employed for Doxorubicin delivery for cancer therapy [30]. For drug delivery, the intercalating area between the alkyl grafts of reducible copolymers and the oleic acid layer on the surface of the nanoparticles stored the hydrophobic drug, while the PEG chains improved the dispersion of the nanoparticles in aqueous environment. The Doxorubicin delivered via these nanoparticles inhibited successfully the growth of xenograft MDA-MB-231 breast tumors in mice. Drug encapsulation in maleimide-polyethyleneglycol-poly(d,l-lactic-co-glycolide) particles (PEG-PLGA) was investigated for targeted drug delivery of Cisplatin [2]. The Cisplatin encapsulating particles were produced using a single step electrospray technique, and were further modified with a CD44 monoclonal antibody targeting the counterpart receptor. Cisplatin-encapsulating CD44-PEG-PLGA particles targeted efficiently CD44-overexpressed ovarian cancer cells, and exhibited an increased anti-proliferative ability at normal chemotherapy concentrations, as compared to the free form of Cisplatin. Polyethyleneglycol-poly (l-lactic-co-glycolic acid) nanoparticles were also employed for targeted drug delivery of Paclitaxel [64]. PEG-PLGA nanoparticles functionalized with an iNGR moiety presented the highest accumulation and deepest penetration at glioma sites. Paclitaxel-loaded iNGR-NP showed promising anti-angiogenesis activity and improved survival time for mice with intracranial glioma.

Micellar drug delivery systems were explored by Xu et al. [63] for delivery of atorvastatin calcium (Ator). Delivery micelles consisted of amphiphilic copolymers of methoxy polyethylene glycol-s-s-vitamin

E succinate (PSV). Ator-loaded PSV micelles showed good colloidal stability, high drug loading, and great encapsulation efficiency. The release of the Ator drug into the cytosol was facilitated by detachment of the PEG shell in the presence of high concentration of intracellular glutathione. The Ator-loaded micelles were shown to inhibit significantly the migration and invasion of 4T1 metastatic breast cancer cells. Dual drug delivery coupled with a targeted approach in a polypeptide-based micelle system was accomplished by Song et al. [58]. The micelle was composed of an amphiphilic copolymer prepared by grafting α -tocopherol and polyethylene glycol onto poly(l-glutamic acid), while the surface of the micelles was modified with an $\alpha v \beta 3$ integrin targeting peptide, c(RGDfK). The incorporation into micelles of two drugs, Docetaxel and Cisplatin, was accomplished via hydrophobic and chelation effects. The drugs co-delivered in micelles showed synergistic cytotoxicity, long circulation time, and enhanced internalization into mouse melanoma (B16F1) cells. Polymeric micelles have also been employed for diagnostic purposes as delivery vehicles for diagnostic reagents. As a first example, Kim et al. [57] developed pH-responsive polymeric micelles loaded with MRI contrast agents for use in cancer diagnostics. Self-assembled micelles made of amphiphilic block copolymers: methoxy polyethylene glycol-b-poly(l-histidine) and methoxy polyethylene glycol-b-poly(l-lactic acid)-diethylenetriaminopentaacetic acid dianhydride-gadolinium chelate, proved stable at physiological pH, but collapsible in acidic conditions due to protonation of imidazole groups. The destabilization of the micelles in the acidic tumoral environment allowed the preferential accumulation of the MRI contrast agent in the tumoral regions, enabling the detection of small tumors within minutes. As a second example, Guo et al. [61] reported the development of PEG-polyaspartamide micelles loaded with a photosensitizer (Ce6) and cyanine dye (Cypate), with a dual role, cancer diagnostics and cancer photo-therapy. Photosensitizer-loaded micelles that also integrated a cyanine dye enabled localizing of the tumors via dual photoacoustic/near-infrared fluorescent imaging, and simultaneously induced photothermal damage to cancer cells by sequential synergistic photothermal /photodynamic therapy.

Applications of Polyethylene Glycol Hydrogels in Wound Healing and Tissue Regeneration

Another major reported use of polyethylene glycols in 2014 referenced papers is for the development of hydrogels [14,19,38-56]. Among the common uses of PEG hydrogels are the use as adhesives for wound closure, as controlled release matrices for therapeutics, for wound healing, as part of medical devices, and as regenerative medicine tools. A biodegradable cyto-compatible bioadhesive hydrogel system was developed by Jeon et al. [47] from an oxidized methacrylated alginate/8-arm polyethylene glycol amine used for culture of human bone marrow-derived mesenchymal stem cells. The swelling behavior, degradation profiles, and storage moduli of the hydrogel bioadhesive were adjusted by varying the degree of oxidation of the alginate. The adhesion level was enhanced on a porcine skin model as compared to commercially available fibrin glue. Another bio-adhesive hydrogel, Catechol-containing 4-armed PEG end-capped with dopamine, was researched by Cencer et al. [55]. Studies on the effect of pH on the rate of intermolecular cross-linking and adhesion to biological substrates allowed the identification of the optimal buffering pH for formulation of the adhesive. When tested as an adhesive for pericardium tissues, a formulation pH of 7.4 provided the ideal balance of curing rate, mechanical properties, and interfacial binding ability for the Catechol-containing 4-armed PEG hydrogel end-capped with dopamine.

Progress on research and development of regenerative therapies aided by PEG hydrogel matrices is reported in several 2014 publications.

As an example, a study by Frith et al. [39] describes a combination of mesenchymal progenitor cells with a potentially injectable PEG/hyaluronic acid degradable hydrogel with a covalently bound pentosan polysulphate, that showed promise as therapy for the regeneration of the cartilage tissue. The molecular weight of the polyethylene glycol chains does not have a significant effect on cell division and sulfated glycosaminoglycan production as part of composite hydrogels [46]. Likewise, for regenerative medicine purposes, Hoffman et al. [48] created a "tissue engineered periosteum", utilizing hydrolytically degradable PEG hydrogels to transplant and localize mesenchymal stem cells to allograft surfaces. The approach increased the autograph healing-graft vascularization, the endochondral bone formation, and the biomechanical strength, when compared to untreated allografts. As a drawback, the process of endochondral ossification was delayed compared to untreated allografts, requiring future supplementation of the hydrogels with additives to expedite the ossification process for treatment of critical sized bone defects. Nguyen et al. [44] controlled the *in situ* osteogenic differentiation of encapsulated stem cells in polyethylene glycol hydrogels by employing localized, and prolonged delivery of siRNA and/or miRNA interfering molecules. Moreover, differentiation of encapsulated human mesenchymal stem cells down the osteogenic lineage was achieved by Hao et al. [14] by *in-situ* cell culture in a 4 arm PEG hydrogel scaffold, by varying the rate and type of the hydrogel degradation. A 4arm PEG hydrogel was synthesized via a mixed-mode step-and-chain-growth photo-polymerization in visible light, using functionalized 4-arm polyethylene glycol as a backbone macromer, eosin-Y as a photosensitizer, a di-thiol containing molecule as co-initiator/cross-linker, and N-vinylpyrrolidone (NVP) as a gelation accelerator. The gelation kinetics, gel degradation, swelling and stiffness, were dependent on the identity of the functional groups, the identity of the cross-linkers, as well as on the concentration of the cross-linker and NVP.

Applications of Polyethylene Glycol Hydrogels in Cell Culture and Tissue Models

PEG and PEG-copolymer hydrogels are practical solutions as scaffolds and have been used for cell culture; for controlled release of therapeutics; and for various other applications, including but not limited to tissue engineering. PEG hydrogels with physiologically relevant matrix elasticities and diffusion distance, fabricated in transwell inserts, were utilized by Gould et al. [38] for cell culture of valvular interstitial cells and valvular endothelial cells. Growth of the cells in the PEG hydrogel matrices has enabled relevant investigations related to aortic valve stenosis initiation and progression. As a replacement to the traditional 2D cell culture techniques for human Pluripotent Stem Cells (hPSCs), Dang et al. [42] proposed polyethylene glycol hydrogels as cell growth scaffolds, with the addition of an immobilized soluble angiopoietin-1-derived peptide, QHREDGS. The addition of the peptide enabled a dose-dependent increase in the cell adhesion into a well-defined network, simultaneously inhibiting the apoptosis of hPSCs. The morphology of the human bone marrow stromal cells was demonstrated by Farooque et al. [40] to be closer to physiological conditions in 3D PEG tetramethacrylate hydrogels scaffolds, compared to traditional 2D planar conditions. In another application, Daniele et al. [41] developed a bio-synthetic tissue scaffold consisting of an interpenetrating network of gelatin methacrylamide polymerized within a polyethylene glycol framework for the culture of endothelial cells. This tissue model showed extensive cytoplasmic spreading and cellular adhesion, with sustained viability and proliferation for encapsulated and adherent cells.

Lin et al. [45] developed an orthogonal thiol-ene PEG hydrogel system for cell culture of liver cell lines, Huh7 and HepG2. The hydrogel system was based on a poly(ethylene glycol)-tetra-norbornene macromere, which allowed facile incorporation of bioactive peptides (e.g., fibronectin-derived RGDS) for improved cell-matrix interactions. According to the authors, this 3D hydrogel system is the first to up-regulate the expression of NCTP in encapsulated Huh7 and HepG2 cell lines and the hepatocyte-like polarity, without genetic modification, and without the need for growth factors and chemical additives. The effect of substrate stiffness on the responsiveness of melanoma cells to treatment with a pharmacological inhibitor, PLX4032, was studied by Tokuda [43] on cell cultures on PEG hydrogel. The use of PEG hydrogels revealed stage-dependent responses to PLX4032 that were not detectable in traditional culturing techniques. For example, the researchers have demonstrated that A375 cells' response to treatment does not depend on the stiffness of the tissue; whereas WM35 cells are more dependent on the substrate modulus, displaying increased apoptosis and decreased focal adhesions on the substrate. Zhang [49] determined that larger amounts of ammonia cross linker used in the polymerization of an 8 arm PEG macromere, lead to higher cross-linking density and bulk of hydrogels, an increased surface elasticity and, generally, to smoother surface morphologies. The amount of cross linker is therefore important in the polymerization of PEG-based hydrogels formed by amine-Michael type addition.

Conclusions

Several noteworthy research papers published in the first half of 2014 were reviewed in detail in this publication, describing the use of polyethylene glycols and PEG hydrogels in cancer diagnostics and drug delivery, wound healing, tissue regeneration, cell culture, and as tissue scaffold models. Other applications of polyethylene glycols reported in early 2014 are summarized briefly in Table 1, including for PEGylation of small and large molecules, such as peptides, proteins, folate, mannose, oligonucleotides; PEGylation of cells, nanoparticles and virus particles; and for surface modification.

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