Current Opinion in Colloid & Interface Science 31 (2017) 51–66

Contents lists available at ScienceDirect

Current Opinion in Colloid & Interface Science

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

Feasibility of polymer-drug conjugates for non-cancer applications

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ARTICLE INFO

Article history:
Received 21 May 2017
Received in revised form 27 July 2017
Accepted 28 July 2017
Available online 12 August 2017

Keywords:
Non-cancer disease
Polymer-drug conjugate
Macromolecular prodrug
EPR effect
Targeted drug delivery'
Inflammation
Cardiovascular diseases

ABSTRACT

Polymer-drug conjugates have been intensely studied in the context of improving cancer chemotherapy and yet the only polymer-drug conjugate on the market (Movantik®) has a different therapeutic application (relieving opioid-induced constipation). In parallel, a number of studies have recently been published proposing the use of this approach for treating diseases other than cancer. In this commentary, we analyse the many and very diverse applications that have been proposed for polymer-drug conjugates (ranging from inflammation to cardiovascular diseases) and the rationales underpinning them. We also highlight key design features to be considered when applying polymer-drug conjugates to these new therapeutic areas.

1. Introduction

Pioneering work on polymer-drug conjugates (PDC)s started in the 1950s [1•], but it was only in 1975 that the concept of PDC as a means of achieving drug targeting was formalised by Ringsdorf [2••]. Since then, research in this field has traditionally focussed on their applications in cancer to enhance the delivery of chemotherapeutic agents to tumour tissues. Interestingly, whilst a number of conjugates progressed to clinical trials with some reaching Phase 3 [3••,4], the only polymer-drug conjugate on the market (PEG-naloxone, naloxegol, Movantik®) is actually used for a different therapeutic application (to treat opioid-induced constipation) [5]. PEG-naloxone is a conjugate in which a PEG oligomer (7 units, MW of <1 kDa) and drug molecules (naloxone) are covalently attached *via* a linker [6]. However, the rationale for this system (and its subsequent application) is fundamentally different from that of traditional polymer-drug conjugates (see Fig. 1). For example, in traditional polymer-drug conjugates the purpose of the polymer is to increase selective accumulation in the tumour through passive accumulating in the tumour tissue, by the enhanced permeability and retention effect (EPR) [7••,8]. In Movantik®, however, the PEG is incorporated to prevent naloxone from penetrating through the blood-brain barrier, hence maximising its peripheral effects [5].

Whilst many reviews focus on the use of polymer-drug conjugates for cancer, the application of polymer-drug conjugates for non-cancer diseases has been less widely reviewed [9••,10]. This review therefore critically appraises the application of PDCs in diseases other than cancers, with a focus on the rationales and the key considerations that have underpinned their design (Tables 1 and 2), with information summarised according to the therapeutic area. We finish the commentary with some general considerations about this emerging field.

2. Polymer-drug conjugates in diseases other than cancer

The strategy of conjugating low molecular weight drugs to polymeric carriers has been applied in order to develop novel therapeutic systems towards diseases other than cancer. These applications include infections, inflammation, nervous system diseases, cardiovascular disease, endocrine disease, digestive diseases, bone problems, eye diseases, and wound-related problems as summarised in Table 2. In these cases, PDCs have generally been developed in order to overcome limitations associated with therapeutically active drugs that are typically used in

Abbreviations: AHPP, 4-Amino-6-hydroxypyrazolo[3,4-D]pyrimidine; Apaf-1, Apoptotic protease activating factor 1; AsnPhePhe, Asparagine-phenylalanine-phenylalanine; D-(Asp)8, D-Aspartic acid peptide; D, Degradable; E, Enzymatic degradation; H, Hydrolytic degradation; EDTA, Ethylenediaminetetraacetic acid; G, Generation; GFAL, Glycine-phenylalanine-alanine-leucine; GFGG, Glycine-phenylalanine-glycine-glycine; GFLG, Glycine-phenylalanine-leucine-glycine; GG, Glycine-glycine; 4G, Glycine-glycine-glycine-glycine; GGPNle, Glycine-glycine-proline-norleucine; GL, Glycine-leucine; HEMA, 2-Hydroxyethyl methacrylate; HPMA, *N*-(2-hydroxypropyl)methacrylamide; I/R, Ischemia reperfusion; Lact2G, Lactic acid-glycine-glycine; Lact4G, Lactic acid-glycine-glycine-glycine-glycine; LMHC, Low molecular weight hydroxyethyl chitosan; N/A, Not applicable/Not stated; OR, Oxidation responsive; PAA, Poly(acrylic acid); PAHA, Poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)]-poly[α,β-(*N*-2-aminoethyl-DL-aspartamide)]; PAMAM, Poly(amidoamine); PCL, Polycaprolactone; pDMAEMA, Poly(dimethylamino)ethyl methacrylate; PEG, Poly ethylene glycol; mPEG, methoxy PEG; sPEG, star PEG; PGA, Polyglutamic acid; PHEA, α,β-poly [(*N*-2-hydroxyethyl)-DL-aspartamide]; PHPA, Poly[α,β- (*N*-3-hydroxypropyl-DL-aspartamide)]; PHPMA, Poly *N*-(2 hydroxypropyl)methacrylamide; PMAA, Poly(methacrylic acid); PVP, Poly(vinylpyrrolidinone); SMA, Styrene-maleic acid.

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http://dx.doi.org/10.1016/j.cocis.2017.07.004
1359-0294/

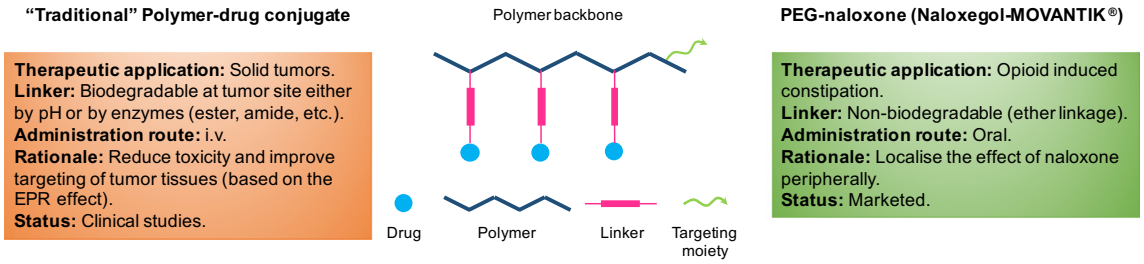

Fig. 1. Schematic diagram of PDCs and key differences between traditional PDCs for cancer and the PDC on the market.

these diseases, for example, poor solubility, undesirable pharmacokinetic properties, or low bioavailability at the disease site.

2.1. Polymer-drug conjugates as polymer therapeutics for infections

2.1.1. Antibiotics

PDCs of different antibacterial agents have been developed in order to enhance their therapeutic activity against different types of bacteria, as summarised in Table 2. Three main aims were explored in these studies, specifically: a) to provide a sustained release of the drug which led to a reduced toxicity, b) to selectively target the drug to the desired site of action, c) to extend the $t_{1/2}$ of the drug. The first studies in this area were reported in the 1960s where water-soluble polymeric derivatives of various penicillin antibiotics using polyvinylpyrrolidone were developed [25–27]. Later, in a study reported in 1989, the aim was to reduce toxicity associated with the administration of isoniazid against *Mycobacterium tuberculosis* by developing a system for the sustained release of isoniazid. Isoniazid was linked *via* an amide bond to poly-α,β aspartic acid [12] and to poly($_{DL}$-succinimide) [13]. The poly($_{DL}$-succinimide)-isoniazid conjugate exhibited a delayed release of the isoniazid in the simulated gastric environment pH (1.2) due to the gradual degradation of the amide linkage *in vitro* [13]. A similar approach was used also for Peptoid 7, a small molecule with an ability to neutralize lipopolysaccharides and potentially treat septicaemia, to provide a controlled release of this drug and again to improve its safety profile [15]. Peptoid 7 was linked to PGA and PEG *via* different spacers: the dipeptide GG with or without lactic acid (Lact) through amide and ester bonds, respectively. *In vitro* release studies indicated that the conjugates were stable plasma, but released the drug after exposure to cathepsin B.

The second rationale for employing conjugation was to enhance the targeting of antibiotics to specific cells and tissues depending on different mechanisms. Azithromycin was linked *via* an ester bond to PAMAM G4 dendrimers to increase the delivery of azithromycin and to improve its antibacterial activity against *Chlamydia trachomatis* [21]. The design of the conjugate was based on the ability of dendrimers to accumulate in inflamed tissues (such as chlamydial arthritis) due to the leaky vasculature of the area. This allows accumulation of macromolecules which is enhanced further as a result of the dendrimer's affinity for glucosaminoglycan released in the inflamed tissues [28–31]. *In vitro* studies indicated high uptake of the fluorescently-labelled azithromycin dendrimers by the *Chlamydia trachomatis* infected human epithelial type 2 (HEp-2) cells in both acute and persistent states of infection with high localisation of the dendrimers in the inclusions.

In other studies, selective accumulation at the infected site was achieved by using targeting moiety rather than exploiting the natural accumulation of the systems in the tissues. As mannose receptors are expressed on the surface of the macrophages [32], conjugates of norfloxacin were grafted with mannose moieties to increase accumulation in macrophages infected by *Mycobacterium tuberculosis* bacilli. The effectiveness of the strategy was the proven *in vivo* (*M. bovis* BCG infected mice), where, unlike the non-mannosylated conjugate, the mannosylated conjugate was effective against isoniazid-insensitive mycobacteria in the liver, spleen, and lung [17,18]. Other targeting ligands have been suggested such as a carboxymethylation of glucan to target T.B infected macrophages [19]. One particularly interesting example of the actively targeted conjugate is PAMAM (G3)-LED209 for Gram negative bacterial infection. In this case, LED209 had a dual role as an active drug and as a targeting ligand [20]. The mechanism of action of LED209 is based on the allosteric alteration of lysine residues of QesC which, consequently, impairs the function of QesC and significantly reduces the virulence of the pathogens. QesC is a histidine sensor kinase that is found in at least 21 Gram negative bacteria that induce infection in humans and also plays an important role in activating the expression of the virulence genes in these pathogens. Moreover, LED209 does not display toxicity and does not influence the bacterial growth [33]. *In vitro* analysis demonstrated greater accumulation of the LED209-dendrimers in the *bacteria* cells than in mammalian SW480 cells. Furthermore, G3 PAMAM-LED209 significantly inhibited the expression of virulence genes in *EHEC* and *S. typhimurium*, and displayed potent antibacterial activity against susceptible and resistant Gram negative bacteria.

The third rationale for applying a PDC strategy for antibacterial usage was to address unfavourable pharmacokinetic properties of certain antibiotics. For instance, vancomycin is a glycopeptide antibiotic that requires infusion every 6 h to obtain effective therapeutic levels due to renal elimination ($t_{1/2}$ of 4.8 h) [34]. PEG-vancomycin conjugates were prepared to increase the mean residence time of the drug in the blood stream by reducing the renal excretion with a size exclusion mechanism [23]. All conjugates showed antibacterial activity against *S. aureus* in infected mice. Furthermore, all conjugates exhibited high AUC with a range of 171–2184 h·μg/mL in comparison with native vancomycin (78.8 h·μg/mL), which indicated that the conjugate might require less frequent administration than the free drug.

Table 1
Rationales for applying PDCs to non-cancer diseases and the mechanisms.

Rationale	Mechanism
R1: Controlled/sustained release (with respect to time)	a) pH-dependent release b) Enzyme-dependent release
R2: Increase water solubility	Linking to a water-soluble polymer
R3: Enhance targeting/controlled release (with respect to space)	a) Receptor-mediated activation b) Tissue affinity/tropism c) pH/GSH/ROS mediated activation d) Enzyme-mediated activation e) Specific feature of vasculature ("EPR-like effect")
R4: Enhance stability and prolong $t_{1/2}$	a) Reduce renal filtration b) Reduce chemical or enzymatic degradation c) Prevent photosensitivity
R5: Combination therapy	a) Polymer and drug have therapeutic effects b) Loading of two drugs
R6: Localised effect	Prevent BBB penetration or keep at the site of administration

2.1.2. Antifungal

The rationales behind the application of a conjugation strategy within the context of treating fungal infections are mainly to reduce the toxicity of the drug by increasing water solubility, and/or to enhance the selective drug targeting to the fungal infected tissues and increase drug accumulation (which is based on the specific environmental pH