Polymer–drug conjugates: present state of play and future perspectives

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Polymer conjugation is an efficient approach to improve therapeutic properties of drugs and biological agents. Since the first synthetic polymer–drug conjugate entered clinical trials in 1994, this technology has undergone notable development for the introduction and study of novel polymers and for the progress in the biological rationale for designing conjugates. Not surprisingly, new polymers, in addition to the best known polyethylene glycol, poly[*N*-(2-hydroxypropyl)methacrylamide], are continuously conjugated with drugs to achieve biodegradable, stimuli-sensitive and targeted systems in an attempt to prolong blood circulation times and enhance drug concentrations at the intended site of action. This overview focuses on bioconjugates of water-soluble polymers with low molecular weight drugs. Additionally, the most recent achievements in the polymer–drug conjugate field and several promising approaches for the future are discussed.

Introduction

Polymer–drug conjugates belong to an area of polymer therapeutics where the common feature is that the therapeutic agent is not encapsulated but covalently linked to a polymeric macromolecular carrier [1,2]. It was initiated nearly 60 years ago. Jatzkewitz pioneered conjugation of mescaline to poly(vinyl prrolidone) (PVP) via a dipeptide spacer in 1955 [3]. Subsequently, numerous polymer–drug conjugates were designed and synthesized, reviewed in [1,4]. Until the mid-1970s, a clear model for polymer–drug conjugates had been proposed by Ringsdorf [5]. Then, in the late 1970s and early 1980s Duncan's research with Kopecek and colleagues produced the first synthetic conjugate to progress to clinical trials, reviewed in [6–8]. According to the Ringsdorf model, an ideal polymer–drug conjugate is characterized by a biocompatible polymer backbone as a vehicle and bioactive agent(s) usually bound to the polymeric scaffold via a biologically responsive linker. Sometimes, a targeting moiety or a solubilizer can also be introduced into the conjugate to improve the therapeutic efficiency.

Inspired by this, many steps have been made in developing novel drug delivery systems. In general, the conjugation of hydrophilic polymers will deeply change the behavior of the corresponding parent drugs. Compared with the parent drug, the main advantages of polymer–drug conjugates are: (i) dramatically increased aqueous solubility of the hydrophobic drugs; (ii) a potential for drugs to be delivered in a triggered release manner under certain conditions, such as a change in pH or in the presence of specific enzymes; (iii) improvement in drug bioavailability and a more prolonged plasma half-life; (iv) protection of drugs against degradation; (v) altered biodistribution and specific accumulation in organs, tissues or cells by targeting agents or the known enhanced permeability and retention (EPR) effect [9]. With the above-mentioned advantages, the polymer–drug conjugates start a new era of drug delivery systems. In these conjugates, most pendant drugs are highly hydrophobic causing the conjugate to self-assemble as a nanosized, unimolecular micelle conformation in aqueous phase (typically 5–20 nm). Moreover, with the advent of 'nano', it has become popular to use the macromonomers to adopt polymeric nanoparticles and polymerosomes typically much larger (>30–50 nm) in size.

Indeed, the task of acquiring a successful polymer–drug conjugate seems intricate. Various factors should be considered during the design. Selection of polymeric macromolecular carriers, desired target (intracellular, lymphatic system, etc.), type of conjugation (direct or indirect), linker chemistry and the molecular weight (MW) can be thought of as the key parameters. Moreover, it

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TABLE 1

Polymer–drug conjugates present in clinical trials.

Conjugates	Drug name	Company	Indication	Status
PEG-naloxol	NKTR-118	Nektar	Opioid-induced constipation	Phase III
PEG-irinotecan	NKTR-102	Nektar	Solid tumor	Phase III/II
PEG-SN38	EZN-2208	Enzon	Solid tumor	Phase II
PEG-docetaxel	NKTR-105	Nektar	Solid tumor	Phase I
PHPMA-doxorubicin	PK1 (FCE28068)	Pfizer	Breast cancer, lung cancer, colorectal cancer	Phase II
PHPMA-platinum	AP5280	Access Pharmaceuticals	Various malignancies	Phase II
PHPMA-DACH-oxaliplatin	ProLindac™ (AP5346)	Access Pharmaceuticals	Ovarian cancer	Phase II
Fleximer®-camptothecin	XMT-1001	Mersana	Gastric cancer, lung cancer	Phase I
Carboxymethyl dextran-T2513	Delimotecan (MEN 4901/T-0128)	Daiichi Pharmaceuticals	Various malignancies	Phase I
Cyclodextrin-camptothecin	CRLX101	Cerulean	Advance solid tumor	Phase IIa
Polyglutamic acid-paclitaxel	Xyotax™, Opaxio™, CT-2103	Cell Therapeutics	Lung cancer, ovarian cancer	Phase III
Polyglutamic acid-camptothecin	CT-2106	Cell Therapeutics	Colon cancer, ovarian cancer	Phase I/II

should be noted that the design of an appropriate polymer carrier must be strongly influenced by its proposed route of, and frequency of, administration and dose. Although several polymer–drug conjugates have shown considerable promise in clinical trials over the past years, the first marketed product is still awaited. Problems that are impeding further development include: polymer-related toxicity (e.g. cytotoxicity, hematotoxicity, complement activation, carcinogenicity, teratogenicity and cellular and humoral immunogenicity); limited drug loading or unsuitable choice of drug (usually bioactivity too low); inadequate linker chemistry (being either too stable to release drug at an appropriate rate on arrival within target cells or degrading too quickly, therefore leading to premature drug liberation during transport); and pharmacoeconomic considerations, reviewed in [10,11]. For instance, clinical failures in the cases of PCNU166148™ and PNU166945™ were caused by an incorrect conjugate rational design that resulted in unspecific drug release. Moreover, poor activity with Opaxio™ in early Phase III trials or commercial issues found in FCE28068 and FCE28069 have been some of the problems responsible for marker vacancy. Unequivocally, this predicament will eventually be improved following the growing number of conjugates entering clinical trials (Table 1).

In this review, we focus on bioconjugates of water-soluble polymers with low MW drugs. An overall coverage of the field of polymers with different chemical properties and architectures is reviewed, providing a preliminary overview on polymer–drug conjugates. More importantly, this review presents the exciting and promising field of polymer–drug conjugates in the treatment of multiple types of diseases other than cancer.

PEG–drug conjugates

As one of the most well-known synthetic polymers, polyethylene glycol (PEG) exhibits unique features. It has high solubility in water as well as in many organic solvents. This feature, together with its biocompatibility and commercial availability, has led to it being widely investigated in the field of drug conjugation and delivery: the famous strategy termed PEGylation. Initially, PEGylation was generally used to modify proteins and peptides dating from the 1970s, reviewed in [12]. Subsequently, researchers focused on covalent combinations of PEG with small molecular drugs to overcome low solubility, rapid excretion and untargeted biodistribution, which are the common problems that frequently trouble drug application. However, liner PEG as a drug carrier is intrinsically limited in drug payload owing to the fact that only two hydroxyl terminal groups can be available for the conjugation in PEG backbone. To address this potential shortcoming, several novel dendron structures at the terminal of the PEG chain have been prepared, including branched PEG, forked PEG and multi-armed PEG [13–15] (Fig. 1). According to published papers, branched and forked PEG are preferred in protein PEGylation, not frequently conjugated with small molecular drugs. In this review, we will focus on the active carriers: linear PEG and multi-armed PEG.

Linear PEG

In PEGylation, linear PEG is the simplest and most commonly used conjugate carrier. In these cases, drugs are attached to the end of PEG chain to improve solubility and bioactivity. As a good illustration, NKTR-118 (PEG–naloxol) is the only linear PEG conjugate from the four PEG–drug conjugates undergoing clinical trials. It is currently in Phase III clinical trials being developed as a once-daily oral tablet for the treatment of debilitating conditions such as opioid-induced bowel dysfunction (OBD) and opioid-induced constipation (OIC) (http://www.nektar.com/product_pipeline/cns_pain_oral_naloxegol_nktr118.html). Placebo-controlled Phase II clinical trial results demonstrated oral NKTR-118 attenuated gastrointestinal-related side effects by increasing the frequency of spontaneous bowel movements in patients with opioid-induced constipation, whereas simultaneously there was no apparent reversal of opioid-mediated analgesia (http://ir.nektar.com/releasedetail.cfm?ReleaseID=419043).

Multi-armed PEG

A multi-armed PEG is a star-like structure generally prepared with hexaglycerine at the core and carrying multiple hydroxyl groups for attachment of many small molecular drugs to increase the loading capacity. For PEG–drug conjugate technology, this multi-armed PEG is the most widely used structure, and several outstanding examples, such as EZN-2208 (PEG–SN38), NKTR-102