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Review

Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery

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ABSTRACT

In the past decades, polymeric nanoparticles have emerged as a most promising and viable technology platform for targeted and controlled drug delivery. As vehicles, ideal nanoparticles are obliged to possess high drug loading levels, deliver drug to the specific pathological site and/or target cells without drug leakage on the way, while rapidly unload drug at the site of action. To this end, various "intelligent" polymeric nanoparticles that release drugs in response to an internal or external stimulus such as pH, redox, temperature, magnetic and light have been actively pursued. These stimuli-responsive nanoparticles have demonstrated, though to varying degrees, improved *in vitro* and/or *in vivo* drug release profiles. In an effort to further improve drug release performances, novel dual and multi-stimuli responsive polymeric nanoparticles that respond to a combination of two or more signals such as pH/temperature, pH/redox, pH/magnetic field, temperature/reduction, double pH, pH and diols, temperature/magnetic field, temperature/enzyme, temperature/pH/redox, temperature/pH/magnetic, pH/redox/magnetic, temperature/redox/guest molecules, and temperature/pH/guest molecules have recently been developed. Notably, these combined responses take place either simultaneously at the pathological site or in a sequential manner from nanoparticle preparation, nanoparticle transporting pathways, to cellular compartments. These dual and multi-stimuli responsive polymeric nanoparticles have shown unprecedented control over drug delivery and release leading to superior *in vitro* and/or *in vivo* anti-cancer efficacy. With programmed site-specific drug delivery feature, dual and multi-stimuli responsive nanoparticulate drug formulations have tremendous potential for targeted cancer therapy. In this review paper, we highlight the recent exciting developments in dual and multi-stimuli responsive polymeric nanoparticles for precision drug delivery applications, with a particular focus on their design, drug release performance, and therapeutic benefits.

1. Introduction

In the past decades, polymeric nanoparticles have emerged as a most promising and viable technology platform for targeted and controlled drug delivery [1–3]. These particles like viruses have typically submicron sizes of about 20–250 nm and a stealth surface made of water soluble non-fouling polymers such as poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), dextran, and poly(acrylic acid) (PAA). The preclinical and clinical studies have demonstrated that drug-loaded polymeric nanoparticles confer prolonged circulation time, enhanced accumulation in the tumor sites via the enhanced permeability and retention (EPR) effect, reduced drug side effects, improved drug tolerance, and/or better drug bioavailability [4–6]. It should be noted, nevertheless, that current polymeric nanoparticles based on biodegradable aliphatic polyesters such as poly(ε-caprolactone) (PCL), polylactide (PLA), and poly(lactide-*co*-glycolide) (PLGA) are far from optimal with respect to drug release profile, in which a considerable amount of drug is released upon injection as a result of inadequate stability while drug cannot readily be released from nanoparticles following their arrival at the pathological sites and/or in the target cancer cells due to their slow biodegradation [7,8]. This conflicting drug release behavior is a critical account for decreased *in vitro* and *in vivo* antitumor efficacy of drug-loaded nanoparticles.

Various environment-sensitive polymeric nanoparticles that dissolve, swell or collapse in response to an internal stimulus (*e.g.* pH, glucose, redox potential, and lysosomal enzymes) or external

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stimulus (*e.g.* temperature, magnetic field, ultrasound, and light) have been actively developed to accomplish enhanced drug release at the target site (spatial control) and/or at the right time (temporal control) [9–11]. For example, taking advantages of slightly acidic environments in cancerous tissues (pH 6.5–7.2), endosomes (pH 5.0–6.5) and lysosomes (pH 4.5–5.0) as compared to physiological pH of 7.4 in the blood and normal tissues, pH-sensitive nanoparticles have been designed and developed to release drugs in the tumor site and/or endo/lysosomal compartments [12,13]. The high redox potential in the cytosol and cell nuclei that contain 100–1000 times higher concentration of reducing glutathione (GSH) tripeptide than body fluids including blood and extracellular milieu (0.5–10 mM *versus* 2–20 μM GSH) have recently been exploited for active intracellular release of various drugs [14–16]. It should further be noted that tumor tissues are highly hypoxic with at least 4-fold higher GSH levels relative to normal tissues [17]. These internal stimuli-responsive nanoparticles have the advantages of self-controlled drug release and facile application in the clinical settings. The external stimuli-responsive nanoparticles, on the other hand, offer obvious merits of precision spatial, temporal as well as dose control over drug release through a remote apparatus, in which drug release might be switched on and off at will [18]. For instance, various light in particular near infrared (NIR)-sensitive polymeric nanoparticles have been designed for triggered anti-cancer drug release *in vitro* and *in vivo* [19]. A number of temperature-responsive nanoparticles have been developed based on thermal-sensitive polymers such as poly(*N*-isopropylacrylamide) (PNIPAAm) and its copolymers [20,21]. Magnetic-sensitive polymeric nanoparticles have been explored for remotely controlled drug release as well as a combination of cancer therapy and diagnosis (theranosis) [22,23].

These stimuli-responsive polymeric nanoparticles have demonstrated improved drug release behavior and anti-tumor activity to varying degrees, depending on type of stimulus, rate of response, and exact spot of triggering drug release. In an effort to further fine-tune drug release and augment therapeutic efficacy of nanoparticulate drugs, sophisticated polymeric nanoparticles that respond to dual and multi-stimuli such as pH/temperature, pH/redox, pH/magnetic field, temperature/reduction, double pH, pH and diols, temperature/magnetic field, temperature/enzyme, temperature/pH/redox, temperature/pH/magnetic, pH/redox/magnetic, temperature/redox/guest molecules, and temperature/pH/guest molecules have been aggressively pursued. It should be noted that the responses take place either simultaneously at the same location or in a sequential manner in different settings and/or compartments. These dual and multi-stimuli responsive polymeric nanoparticles might on one hand offer unprecedented control over drug delivery and release leading to superior *in vitro* and/or *in vivo* anti-cancer potency, and on the other hand also facilitate nanoparticle preparation and loading of drugs under mild conditions. For example, redox-sensitive drug release polymersomes have been developed based on temperature and reduction dual-responsive PEG-PAA-PNIPAAm triblock copolymers by simply increasing solution temperature to above their lower critical solution temperature (LCST) followed by crosslinking with cystamine via carbodiimide chemistry [24,25]. These crosslinked polymersomes while robust against physiological conditions were rapidly dissociated to release exogenous proteins in cancer cells due to redox-triggered de-crosslinking and disruption of polymersomes. pH and redox dual-sensitive disulfide-crosslinked micelles were developed to reduce premature drug release in blood circulation, enhance drug accumulation in the tumor site, and actively release drug in the target tumor cells in response to endo/lysosomal pH and intracellular reducing environment [26]. In this paper, we highlight up-to-date design and preparation of dual and multi-stimuli responsive polymeric nanoparticles and their emerging applications in controlled drug delivery in particular for cancer treatments (Fig. 1). These two and more stimuli are combined in order to: (i) facilitate preparation of nanoparticles under mild conditions through application of an external stimulus such as temperature and pH; (ii) trigger drug release via application of an external stimulus such as magnetic field, ultrasonic, light, and temperature; (iii) trigger drug release or reverse deshielding of nanoparticles thereby enhancing tumor cell uptake of nanoparticulate drugs in a mildly acidic tumor microenvironment; and/or (iv) boost intracellular drug release in tumor cells under endo/lysosomal pH and/or cytosolic reductive conditions. An overview of dual-responsive polymeric nanoparticles for drug release is presented in Table 1.

2. pH and temperature dual-responsive nanoparticles

pH and temperature-responsive nanoparticles are among the most studied dual-sensitive nanosystems. Many pH and temperature-responsive polymers are designed and prepared by incorporating pH-sensitive components such as weak acids into thermo-sensitive PNIPAAm, which affords copolymers with pH-dependent LCST. This fine-tuning of phase transition by subtle pH change has enabled development of tumor pH-sensitive drug release systems. Yang et al. reported that pH and temperature-sensitive core–shell nanoparticles self-assembled from poly(-NIPAAm-*co*-*N*,*N*- dimethylarylamide-*co*-10-undecenoic acid) (P(NIPAAm-*co*-DMAAm-*co*-UA)) terpolymer were stable in a normal physiological condition (pH 7.4, 37 °C) while deformed and precipitated in an acidic environment [27]. The *in vitro* release studies showed that doxorubicin (DOX) was released much faster at mildly acidic pH of 6.6 (simulating tumor microenvironment) than at pH 7.4. The conjugation of cholesterol to the hydrophobic segment of P(NIPAAm-*co*-DMAAm-*co*-UA) and folic acid to the free amine group yielded stable and tumor-targeting nanoparticles that efficiently delivered and released DOX into folate-receptor over-expressing cancer cells including 4T1 and KB cells, resulting in further improved anti-tumor activity [28]. Jiang et al. constructed thermo and pH dual-responsive nanoparticles based on poly(-NIPAAm-*co*-acrylic acid)-*b*-PCL (P(NIPAAm-*co*-AA)-*b*-PCL) diblock copolymer [29]. Interestingly, these nanoparticles could encapsulate up to 30 *wt.*% of paclitaxel (PTX) and aggregated at pH 6.9 and 37 °C. Faster drug release was observed at higher temperature and lower pH. Hsiue et al. reported that temperature and pH dual-responsive micelles based on a mixture of methoxy-PEG-*b*-P(*N*-(2-hydroxypropyl) methacrylamide dilactate)-*co*-(*N*-(2-hydroxy propyl) methacrylamide-*co*-histidine) (mPEG-*b*-P(HPMA-Lac-*co*-His)), mPEG-*b*-PLA and cy5.5-PEG-PLA copolymers displayed a specific targeting efficiency and an improved *in vivo* anti-tumor activity as compared to free DOX in Balb-c/nude mice bearing human cervical tumors [30]. The high anti-tumor activity of DOX-loaded dual-responsive nanoparticles was attributed to their tumor-specific accumulation, enhanced permeation through the tumor site, and tumor pH-triggered drug release.

pH and temperature dual-sensitive nanoparticles have also been developed for efficient drug release under endosomal or lysosomal pH conditions. Hsiue et al. reported that pH and thermo-responsive nanoparticles based on biodegradable poly(D,L-lactide)-*g*-poly(-NIPAAm-*co*-methacrylic acid) (PLA-*g*-P(NIPAAm-*co*-MAA)) graft copolymers had an LCST above 37 °C and a high loading of 5-fluorouracil (5-FU) [31]. The release of 5-FU was significantly enhanced at pH 5.0 than at pH 7.4 as a result of pH-triggered collapse of P(NIPAAm-*co*-MAA) shells. Li et al. reported that pH and temperature-responsive micelles based on biodegradable P(NIPAAm-*co*-DMAAm)-*b*-PLA and P(NIPAAm-*co*-DMAAm)-*b*-PCL