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Review

Polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy: Recent advances in drug delivery

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ABSTRACT

In the last decade, considerable attention has been devoted to the use of biodegradable polymeric materials as potential drug delivery carriers. However, bioavailability and drug release at the disease site remain uncontrollable even with the use of polymeric nanocarriers. To address this issue, successful methodologies have been developed to synthesize polymeric nanocarriers incorporated with regions exhibiting a response to stimuli such as redox potential, temperature, pH, and light. The resultant stimuli-responsive polymeric nanocarriers have shown tremendous promise in drug delivery applications, owing to their ability to enhance the bioavailability of drugs at the disease site. In such systems, drug release is controlled in response to specific stimuli, either exogenous or endogenous. This review reports recent advances in the design of stimuli-responsive nanocarriers for drug delivery in cancer therapy. In particular, the synthetic methodologies investigated to date to introduce different types of stimuli-responsive elements within the biomaterials are described. The sufficient understanding of these stimuli-responsive nanocarriers will allow the development of a better drug delivery system that will allow us to solve the challenges encountered in targeted cancer therapy.

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1. Introduction

Cancer; comprising over 80 diseases; is characterized by the uncontrolled growth of abnormal cells with the potential to spread to other parts of the body (Pérez-Herrero and

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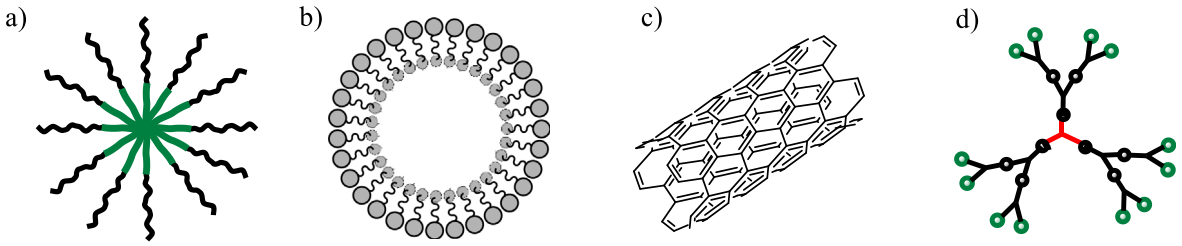

Fig. 1. Different types of nanocarriers for drug delivery systems in cancer therapy. (a) Polymeric micelles, (b) liposomes, (c) carbon nanotubes, and (d) dendrimers.

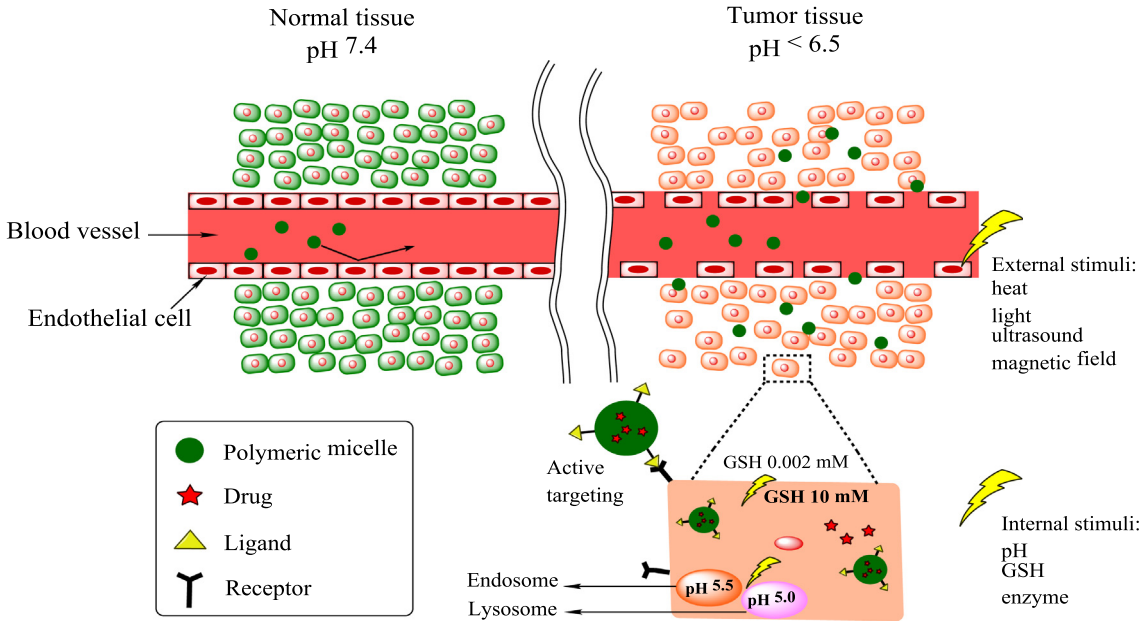

Fig. 2. Transport of stimuli-responsive polymeric nanocarriers through normal (left) and tumor (right) tissues *via* several stimuli-responsive delivery strategies.

Fernández-Medarde, 2015). Despite the availability of several therapies (chemotherapy, radiation, and/or surgery), effective cancer treatment remains a considerable challenge. The endurance of chemotherapy as one of the most efficient methods for cancer therapy has led to the design of numerous efficacious chemotherapeutic anticancer drugs such as doxorubicin and paclitaxel, which destroy rapidly dividing cancer cells *via* damage to their RNA or DNA (Laginha et al., 2005). However, the therapeutic potential of these drugs is limited by their cytotoxicity, which lacks specificity to cancer cells thereby causing serious damage to normal cells. Consequently, it is necessary to develop alternatives such as nanotechnology-based targeted drug delivery systems to decrease the side effects of these drugs and enhance their therapeutic utility.

Over the last decade, various types of drug delivery systems with different designs have been investigated for cancer treatment, including polymeric micelles, liposomes, dendrimers, and carbon nanotubes (Fig. 1) (Sun et al., 2014). Among these, polymeric carriers have attracted considerable attention for cancer therapy owing to their tunable core-shell structure that can be used to physically encapsulate or chemically conjugated drugs within their core (Oerlemans et al., 2010; Torchilin, 2007; Yokoyama, 2010). These polymeric nanocarriers, when designed to be responsive to specific external stimuli, are considered as highly promising drug delivery carriers. Furthermore, these systems increase the solubility limit of drugs, improve drug pharmacokinetics, and facilitate their accumulation in tumors through the enhanced permeability and retention (EPR) effect (Fig. 2) (Maeda et al., 2000; Prabhakar et al., 2013), which is a distinct characteristic of most tumors that allows the preferential accumulation of polymeric nanocarriers of particular sizes in tumor compared to normal tissues.

Ideally, drug nanocarriers should not only solubilize hydrophobic anticancer drugs but also remain in regular circulation for a prolonged period to be introduced into tumor tissue and thus improve the efficacy of cancer therapy (Liu et al., 2014; Torchilin, 2009). Coating the surface of nanocarriers with a hydrophilic polymer constitutes the most common approach adopted to prolong the circulation time of polymeric nanocarriers in the bloodstream. Poly (ethylene glycol) (PEG) is the polymer most commonly used to coat nanocarriers, a process known as PEGylation (Jiang et al., 2013; Shen et al., 2012; Torchilin, 2009). This approach minimizes nanocarrier interaction with components of biological fluids in the bloodstream and avoids their detection by the mononuclear phagocytic system (MPS) and subsequent clearance by the kidneys (Knop et al., 2010; Masood, 2016).

However, despite the use of polymeric nanocarriers, drug release is still difficult to control. There are certain requirements that the polymeric nanocarriers must meet to afford better efficiency and fewer side effects of cancer therapy. For example, the drug release profiles should be controlled in response to internal factors in the microenvironment of a particular disease, external stimuli, or both in some cases (Joseph and Robert, 1991; Lavon and Kost, 1998). Therefore, polymeric nanocarriers designed to release drug cargo at a convenient site with a fixed rate in response to certain stimuli (known as stimuli–responsive polymers) such as pH, temperature, magnetic field, enzymes, or sonication are particularly appealing. In these so-called "smart" polymers, drug release

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is provoked by several stimuli, with such stimuli-responsiveness increasing the utility of the nanocarriers and allowing enhanced drug delivery to pathological areas. The stimuli that trigger drug release from the nanocarriers can be classified with respect to the associated biological systems into two main categories: internal (e.g. changes in pH, redox gradient, and enzyme concentration) (Duan et al., 2013; Khorsand et al., 2013; Mo et al., 2014; Mura et al., 2013; Zhang et al., 2013) or external (e.g. heat, light, sonication, magnetic field, and electric field, which are artificially applied from outside the body) (Fig. 2) (Mura et al., 2013; Pillay et al., 2014; Sirsi and Borden, 2014; Zhang et al., 2013; Zhao et al., 2011).

Although a variety of nanocarriers are being developed (Ganta et al., 2008; Mignani et al., 2013; R. Ramireddy et al., 2012; Raghupathi et al., 2014), this review is intended to contribute to a better comprehension of the different methodologies adopted to incorporate stimuli-responsive elements within the polymeric nanocarriers for the purpose of cancer therapy, rather than covering the field of stimuli-responsive polymeric nanocarriers in its entirety. In particular, this review focuses primarily on polymeric nanocarriers with stimuli-responsive mechanisms with regard to pH, redox potential, enzymes, light, and temperature as primary stimuli, which will be discussed based on selected examples from the literature.

2. pH-responsive polymeric nanocarriers

The altered value of pH observed in pathological conditions including cancer or inflammation has been widely employed to trigger the release of drug molecules into a desired biological organ (e.g. the gastrointestinal tract) or intracellular compartment (e.g. a lysosome or endosome) (Mura et al., 2013). It has long been known that the pH value of diseased areas such as tumor and inflammatory tissues are intrinsically acidic (pH 6.5), almost one full pH unit below that of normal blood (pH 7.4) (Engin et al., 1995; Helmlinger et al., 2002). In addition, a reduction in pH is noted in intracellular compartments, such as endosomes and lysosomes with pH values of 5.5–5.0, respectively. Such pH gradients can be used to design drug delivery systems that remain stable at physiological pH, allowing minimal leakage of drugs entrapped within the hydrophobic core during the long blood circulation, whereas at the low pH environment the carriers respond and become more disrupted to selectively release their transported anticancer drug at the specific site of action, thereby attaining the targeted antitumor activity (Gao et al., 2010).

To facilitate a response to the acidic microenvironments in tumors, two major strategies have been proposed for the design of polymeric nanocarriers. The first is to use polymers with functional groups that can act as proton donors or acceptors in response to an environmental pH variation. At physiological pH, these polymers remain deprotonated whereas under acidic environments they become protonated, causing structural damage and changing the hydrophobicity of the polymers, which leads to specific release of their payload (Fig. 3a) (Chang et al., 2009; Fleige et al., 2012; Ganta et al., 2008; Lee et al., 2008). Polymers containing ionizable groups including weak acids (i.e. carboxylic acids) or weak bases (i.e. amines) are widely used for fabricating pH-responsive nanocarriers to induce the disruption of polymeric micelles in acidic media at the interior and/or exterior of tumor cells (Kanamala et al., 2016; Wang et al., 2018). For example, carboxylic acid based-polymers are frequently employed to construct pH-responsive polymeric nanocarriers, such as poly (acrylic acid) (PAA), poly (methacrylic acid) (PMAA), and poly (glutamic acid) (PGA) (Bersani et al., 2014; Ding et al., 2012; Miatmoko et al., 2017; Yan and Gemeinhart, 2005). With the use of these polymers, at acidic pH, payload release is triggered by reducing the electrostatic interactions of a cationic drug (such as doxorubicin) and an anionic polymer through the protonation of the polymeric carboxylate groups. For example, Zhang et al. (2016) synthesized

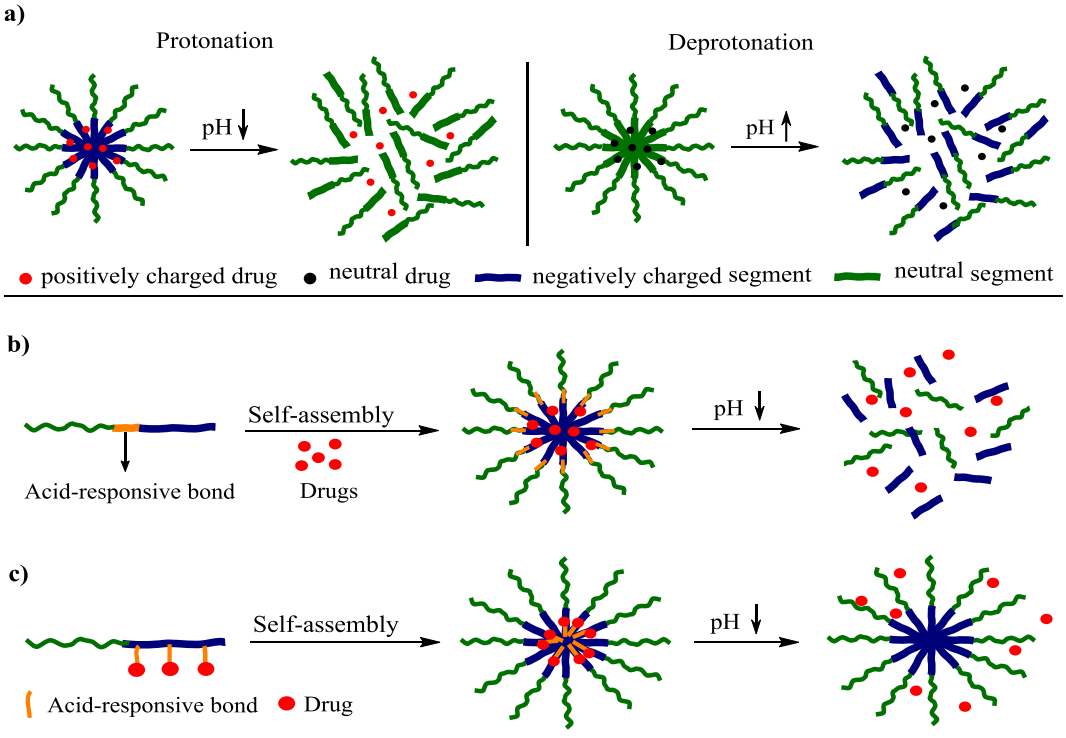

Fig. 3. Schematic illustration of pH-responsive mechanisms for drug release initiated by changes in the pH environment. (a) Protonation (left) or deprotonation (right) of polymers leads to structural damage of the nanocarriers. (b) Breakage of the acid-responsive bonds within the polymer at acidic pH causes damage to the amphiphilic blocks. (c) Breakage of the acid-responsive bond between the anticancer drug and polymer.

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polypeptide-based nanorods comprising anionic methoxy-polyethylene glycol-poly (glutamic acid) (mPEG-PGA) and the positively charged anticancer drug doxorubicin hydrochloride (DOX·HCl) for cancer therapy. Electrostatic interaction between cationic DOX and anionic (mPEG-PGA) polymer was found to generate an efficient drug encapsulation. The block copolymer exhibited an intracellular pH-triggered drug release capability; moreover, the *in vitro* cytotoxicity revealed that DOX-loaded nanorods exhibited higher tumor inhibition compared to that of the free DOX·HCl solution (Zhang et al., 2016).

In addition, polymers bearing amine and imidazole side groups have been extensively utilized to generate micelle-forming copolymers. In particular, amino-based polymers can be deprotonated and are stable during blood circulation, whereas they can be protonated and cause a structural modification in the presence of a biological acidic medium, followed by the considerable release of the captured anticancer drugs (Johnson et al., 2014). Xu et al. (2017) synthesized a pH-responsive poly (ethylene glycol)-b-poly (2-(diisopropylamino) ethyl methacrylate) block copolymer (MPEG-PPDA), which self-assembled to form micelles for the intracellular delivery of DOX. The micelles exhibit considerable stability under normal physiological conditions along with pH-responsive transforming capability between self-assembly and disassembly. A drug release study showed more rapid release at pH 5.0 owing to the total protonation of the amino functionalities, which may cause disassembly of the copolymer micelles. Moreover, the study indicated that the DOX-loaded micelles exhibited higher cytotoxicity compared to that of the free drug (Xu et al., 2017).

The second strategy is to introduce cleavable acid-responsive bonds in the structure of nanocarriers. These bonds between drug and polymer, or within the amphiphilic block copolymers can be broken at acidic pH to specifically release the payload drug conjugated to or encapsulated in the nanocarriers (Fig. 3b, c) (Akita et al., 2013; Binauld and Stenzel, 2013; Du et al., 2013; Felber et al., 2012; Xu et al., 2009). Typical cleavable acid-responsive bonds that can be incorporated into polymeric nanocarriers include hydrazone, hydrazide, imine, acetal, oxime, orthoester, and vinyl ether bonds (Bae et al., 2005; Chen et al., 2009; Gillies and Frechet, 2003; Thambi et al., 2011; Wang et al., 2011). In particular, micelles resulting from the self-assembly of block copolymers can be connected by pH-responsive chemical bonds. In acidic media, the acid-responsive bonds on these polymers, which are usually stable at pH 7.4, become hydrolyzed, thus, disrupting the core-corona micelle structure and releasing the encapsulated drugs (Fig. 3b). For example, Xu, J. et al. (2018) prepared a biodegradable pH-responsive amphiphilic block polymer (mPEG-Hyde-PLGA) that served as a drug delivery system for DOX. The pH-responsive hydrazone linkage was incorporated into the backbone of the block copolymer, connecting hydrophilic PEG and hydrophobic poly(lactic-co-glycolic acid). In vitro release investigations revealed that the release of DOX from the micelles was critically affected by the pH environment owing to the acid-cleavable bond, with faster drug release being observed at pH 4.0 and 5.0 as compared to that at pH 7.4 (Xu, J. et al., 2018). For polymer-drug hybrids, in which the drug is linked to a polymer backbone, the responsive part is usually employed to directly attach drug molecules to the polymer backbone (Fig. 3c). Accordingly, Liao *et al.* (Liao et al., 2018) synthesized hyaluronic acid-hydrazone linkage-doxorubicin (HA-hyd-DOX) through the use of hydrazone linkages as pH-responsive connecting segments for the incorporation of the anticancer drug DOX. At pH 7.4, these hybrids were stable but released the drug at a faster rate at pH 5 (Liao et al., 2018).

Zhao *et al.* (Zhao et al., 2016) exploited the acidic pH environment in gliomas for peptide H7K(R2)2 as a targeting ligand. The H7K(R2)2-modified pH sensitive liposomes containing doxorubicin (DOX-PSL-H7K(R2)2) were designed and evaluated efficiency in glioma tumor cells and in mice with glioma tumor cells. The authors tested *in vitro* release of doxorubicin from pH-sensitive liposomes. The in vivo anti-tumor activity of DOX-PSL-H7K(R2)2 was also evaluated in C6 tumor bearing mice and in U87-MG orthotopic tumor bearing nude mice. The authors reported a specific targeting effect triggered by an acidic pH *in vitro* experiments in C6 and U87-MG glioma cells. The anti-tumor activities of DOX-PSL-H7K(R2)2 were observed in C6 tumor having mice and U87-MG orthotopic tumor having nude mice in in vivo studied. The antiangiogenic activity of DOX-PSL-H7K(R2)2 was also established in C6 tumor having mice. The authors claimed H7K(R2)2-modified pH-sensitive liposomes as promising delivery tool for anti-tumor drug in gliomas.

3. Temperature-responsive polymeric nanocarriers

Temperature-responsive materials have been widely investigated for smart drug delivery applications owing to their phase-transition behavior with regard to variation in temperature. Temperature can either act as an external stimulus (e.g. heat is applied from the outside) or can be internal when the local temperature increase is caused by the pathological condition (e.g. tumor or inflammation). For example, tumor tissues are slightly hyperthermic (i.e. 1–3 °C warmer than normal tissue) (Karimi et al., 2016; Mohammed et al., 2018; Vaupel et al., 1989).

Temperature-responsive polymers display a temperature-dependent phase transition at which they become soluble or insoluble, termed the critical solution temperature (CST). Thermal transition from a more soluble to a less soluble state is defined as the lower critical solution temperature (LCST), with the majority of the temperature-responsive polymers having been synthesized according to this special feature. The swelling variations of the polymers are governed by the hydrophilic/hydrophobic balance of the nanocarrier material (Bae et al., 1990). If the local temperature around the nanocarriers is slightly higher than the LCST, the polymeric chain becomes dehydrated, will, therefore, be more hydrophobic, and then collapse, which triggers the release of the encapsulated drug (Fig. 4). For example, Hu et al. (Hu et al., 2015) prepared the temperature-responsive amphiphilic tri-block copolymers poly[2-(2-methoxyethoxy) ethyl methacrylate-co-oligo (ethylene glycol) methacrylate]-b-poly(L-lactide)-b-poly[2-(2-methoxyethoxy) ethyl methacrylate-co-oligo(ethylene glycol) methacrylate] [P(MEO2MA-co-OEGMA)-b-PLLA-b-P(MEO2MA-co-OEGMA)], which were self-assembled as a temperature-responsive nanocarrier for the hydrophobic anticancer drug curcumin. The experimental results showed that the amount of released drug at 41 °C was almost 20% higher than that at 37 °C (Hu et al., 2015). In another study, Xu, N. et al. (2018) developed a temperature-responsive star polymer polyTEGDA-b-poly-(NIPAM-co-NMA), with poly tetra(ethylene glycol) diacrylate (polyTEGDA) as the hydrophobic core and poly(N-isopropylacrylamide-co-N-methylolacrylamide) (poly(NIPAM-co-NMA)) as the hydrophilic arms. In vitro drug release testing reveal that the release rate was notably increased above the LCST compared to that below the LCST. Moreover, DOX-loaded polymers exhibited better antitumor inhibition toward ovarian carcinoma SKOV3 cells at 42 °C compared to that at 37 °C (Xu, N. et al., 2018).

4. Redox potential-responsive polymeric nanocarriers

Redox-responsive polymeric nanocarriers represent another switchable example of responsive delivery systems with beneficial uses in the application of controlled drug delivery. The redox potential difference between the oxidizing extracellular space and the reducing intracellular space serves as a potential stimulus

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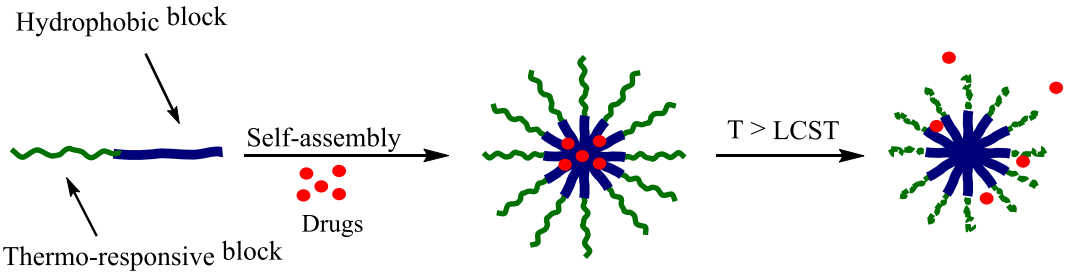

Fig. 4. Schematic illustration of temperature-responsive amphiphilic polymer mechanisms for drug release initiated by a variation in the surrounding temperature. Below the LCST the temperature-responsive shell is hydrated and is hydrophilic. Once the temperature (T) is slightly above the LCST, the hydrophilic corona collapses, which triggers the drug release.

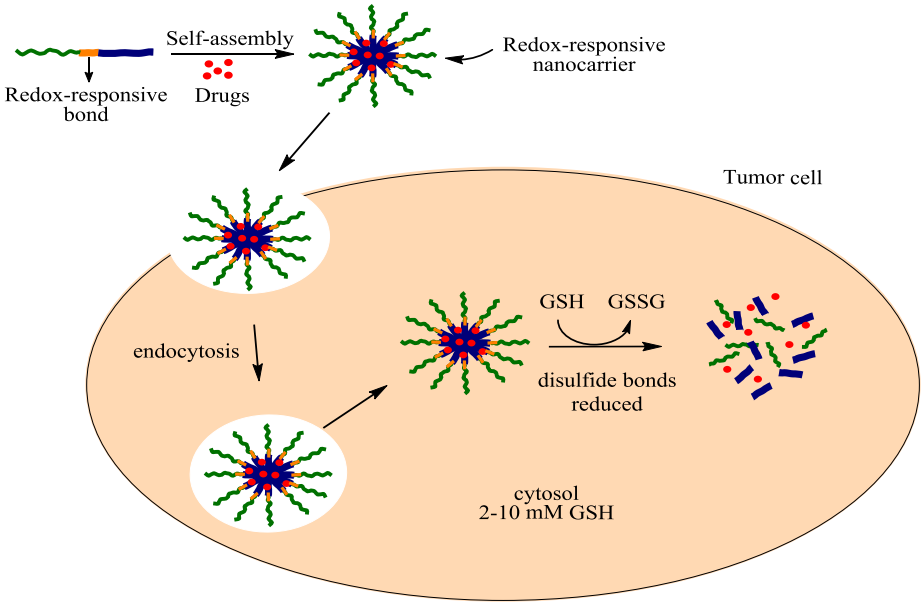

Fig. 5. Schematic illustration of the mechanism of action of redox-responsive micelles. The drug-loaded redox-responsive nanocarrier is taken up into the cancer cell by endocytosis and actively releases the biologically active agent into the cytosol inside the cells owing to GSH-triggered disassembly.

for the triggered release of therapeutics drugs. Notably, owing to the abundance of reduced glutathione (GSH), which has an average extracellular concentration of approximately 2 μm albeit an intracellular concentration of around 10 mm, the cytosol possesses a low redox potential (Huo et al., 2014; Zhang et al., 2017). In addition, the GSH concentration is lower in healthy than in tumor tissues. These differences in redox potential can be employed for redox-responsive intracellular drug delivery. The criteria for design of these redox-responsive polymeric nanocarriers relies on the chemistry of the respective redox-responsive units such as disulfide bonds, which exhibit higher stability in oxidizing extracellular media. In contrast, in a reducing environment, the disulfide bond is reduced to generate thiol groups (Deng et al., 2015; Quinn et al., 2017). Consequently, the polymeric nanocarriers will be disassembled in the presence of the excess glutathione inside the cell, releasing the biologically active agents (Fig. 5). In these systems, a drug can be encapsulated or conjugated to polymeric nanocarriers carrying disulfide bonds. To date, several redox-responsive nanomaterials including block copolymers, dendritic polymers, and redox-responsive biodegradable polymers have been explored (Lv et al., 2018; Teo et al., 2017; Zhuang et al., 2016).

Notably, biodegradable drug delivery nanocarriers can efficiently avoid the poor in vivo metabolism and elimination characteristics of other nanocarrier formulations (Duan et al., 2016). Polymeric nanocarriers with both triggering signals and biodegradability can, therefore, be designed *via* the insertion of disulfide bonds into biodegradable polymers. Recently, Duan et al. (2018) reported an efficient one-pot synthetic method of glutathione-responsive polymeric drug delivery nanocarriers (DOX-DSDA-PEG). Specifically, the Michael addition reaction was adopted to link an aminopolyethylene glycol monomethyl ether (PEG) with DOX and disulfide-based diacrylate (DSDA), and the utility of the redox-responsive properties of these polymeric nanocarriers for tumor therapy was examined. The *in vitro* drug release profiles from these redox-responsive micelles revealed that the DOX release rate could be well controlled by GSH concentration, indicating the potential biomedical application of these on-demand drug delivery systems. After 72 h, and at high GSH concentration (3.25 mM), the release of DOX from the DOX-DSDA-PEG glutathione-responsive nanocarriers reached 67.9%, whereas that without GSH only reached 5.7%. Furthermore, cell uptake and cell viability studies demonstrated that the glutathione-responsive micelles could be taken up by A549 cells and disrupted under high GSH concentration in tumor tissues. These results confirmed that DOX-DSDA-PEG could function as an effective glutathione-responsive drug carrier with biodegradable activities (Duan et al., 2018).

Disulfide bonds can also be used as crosslinking agents that can be incorporated either in the core (Maiti et al., 2018) or the shell (Xiong et al., 2017) of the polymeric micelles, leading to rapid

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disassembly of the polymeric nanosystems followed by the specific intracellular release of drugs. For example, Xia et al. (2018) synthesized polymer-based core-crosslinked redox-responsive nanocarriers (CC-RRNs). In this study, click 1,3-dipolar cycloaddition reaction between the alkyne-based amphiphilic block copolymer PEG-b-poly(MPC)n (PMPC), azide with α-lipoic acid derivative (LA), and 6-bromohexanoic acid derivative (AHE) at different ratios was followed by the introduction of crosslinked networks *via* a catalytic amount of dithiothreitol (DTT) to afford a novel series of CC-RRNs for drug delivery application. Inclusion of a disulfide linkage in the crosslinker enabled the prepared CC-RRNs to be readily degraded by exposure to GSH. Moreover, investigation of the drug release from these redox-responsive CC-RRN nanocarriers concluded that the rate of DOX release from the nanocarriers was dependent on the LA-to-AHE ratio of PMPC-based polymers and the concentration of GSH. At high concentrations of GSH (10 mM), a much faster release rate of DOX from redox-responsive CC-RRNs could be observed.

Lee et al. (2010) exploited the oxidative stimuli-responsive to release camptothecin in gliomas. The authors prepared and characterized the nano prodrug of camptothecin. The nanoprodrug was stimulated quickly by porcine liver esterase and, at a low rate, by hydrolytic degradation. Remarkably, the hydrolytic activation was insignificant prior to the oxidation, but was remarkably increased after α-lipoic acid moiety oxidation; indicating an oxidative stimuli-responsive activation of the prodrug. The camptothecin nano-prodrug was showed a remarkable inhibitory effect on the proliferation of U87-MG glioma cells with an IC_{50} of 20 nM.

5. Enzyme-responsive polymeric nanocarriers

Enzyme-responsive drug release has also attracted considerable interest. Enzymes play a vital role in both biological and metabolic processes inside the human body (Liu et al., 2015). Cancer, which is consider to be one of the most invasive diseases, is characterized by the overexpression of different kinds of enzymes (such as glycosidases and proteases) that are either bound to the membrane or secreted (Hu et al., 2014). The exploitation of enzymes as naturally occurring biological stimuli to trigger the release of a drug by breaking certain bonds and thus causing disassembly or destruction of the micelle structure offers new strategies for the construction of drug delivery systems for cancer therapy (Isaacson et al., 2017).

The design of nanocarriers containing enzyme-responsive properties can be achieved by inserting specific moieties either in the main chain or side groups to generate self-assembled structures, which can be cleaved by a particular enzyme. For example, Zhu et al. (2013) synthesized a PEG2000-peptide-PTX as self-assembling drug-polymer conjugate/prodrug containing a peptide cleavable by matrix metalloproteinase (MMP), an enzyme commonly involved in cancer invasion and metastasis, between PEG and paclitaxel (PTX). In this study, transactivating transcriptional activator peptide (TATp) and phosphoethanolamine (PE) were also used to magnify the target cell internalization and cell penetration and obtain TAT-PEG1000-PE and PEG1000-PE as PTX delivery systems. These nanocarriers not only released the PTX as an active drug but also displayed the hidden TAT for effective cell internalization, which caused the enhancement of both *in vitro* and in vivo anticancer activity.

Lysosomes, as membrane-bound vesicles, possess abundant digestive enzymes including sulfatases and glycosidases (Fehrenbacher and Jaattela, 2005). Therefore, the attachment of drugs with lysosomally cleavable peptides as spacers has also attracted considerable interest (Kopeček and Kopečková, 2010). These nanocarriers are stable during blood circulation but release their payload under the action of certain enzymes. For example, Peng and Kopeček (2015) synthesized a dual enzyme-responsive *N*-(2-hydroxypropyl)-methacrylamide (HPMA) copolymer-DOX conjugate (P-DOX-PLGLAG-iRGD) in which DOX was combined with the HPMA copolymer through GFLG, a cathepsin B cleavable tetrapeptide GFLG spacer, and iRGD was linked to the HPMA copolymer *via* an MMP-2-degradable linker (PLGLAG). This study showed that covalent conjugation of iRGD *via* MMP-2-responsive bonds enhanced the penetration, tumor accumulation, along with cytotoxicity in prostate cancer cells in 2D and 3D culture (Peng and Kopeček, 2015). More recently, Gu et al. (2018) fabricated polytyrosine nanocarriers constructed from poly(ethylene glycol)-b-poly(L-tyrosine) block copolymer that served as enzyme-responsive nanocarriers for DOX. The DOX-loaded nanocarriers achieved a markedly high drug loading content reaching 63.1 wt% and exhibited good colloidal stability under physiological conditions, but were quickly disassembled by proteinase K, increasing the antiproliferative activity compared to that from liposomal DOX formulations against both HCT-116 human colorectal cancer cells and RAW 264.7 cells (Gu et al., 2018). These representative examples highlight the potential of enzyme-responsive nanocarriers in cancer therapy, as compared to those of other stimuli-responsive nanocarriers. Nevertheless, additional work is still required to fully develop such systems; it is hoped that this review will spark novel ideas and motivate continued investigation in this new research area.

6. Light-responsive polymeric nanocarriers

Light-responsive nanomaterials have attracted considerable attention in biomedical applications owing to their non-invasiveness, convenience for on-demand cargo release, and higher potential spatiotemporal resolution (Bertrand and Gohy, 2017; Xiao et al., 2017; Zhou, Y. et al., 2018). Control of the temporal and spatial release relies upon the feature whereby the conjugated/encapsulated therapeutic agents are only delivered when subjected to a high irradiation (UV/visible or near-infrared [NIR] light) external source from outside of the body. The response to light is often introduced in nanocarriers through a linker that can be broken once exposed to light irradiation with a proper wavelength. For example, Jin *et al.* (Jin et al., 2014) synthesized triblock copolymer light-responsive poly(ethylene glycol)-b-poly(ethanedi thiol-alt-nitrobenzyl)-b-poly(ethylene glycol) nanocarriers, which were constructed to have o-nitrobenzyl as a light-cleavable linkage along with acid-labile β-thiopropionate linkages. Loading of DOX led to nanocarriers that exhibited faster drug release and better anticancer activity against A549 cells when exposed to UV light compared to the activities of non-irradiated systems.

In addition to systems involving breaking linkages, UV light has also been exploited as a stimulus to trigger the release of therapeutic agents by disrupting the nanocarriers with the help of a molecular switch such as azobenzene, spirobenzopyran, or nitrobenzene (Rastogi et al., 2018; Sun et al., 2015; Xing et al., 2014). Consequently, marked effort has been devoted to investigating the reversible *cis–trans* isomerization of such compounds, through their irradiation by UV and/or visible light, which induces a change in their polarity. For example, Chen et al. (2011) investigated the post modification methodology to synthesize poly(ethylene oxide)-*block*-poly[(oligoethylene glycol) methacrylate-*random*-(2-diazo-1,2-naphthoquinone oligoethylene glycol) methacrylate] (PEO-*b*- P(OEGMA-*r*-DNQMA). The irradiation of the micelles by UV light at 365 nm resulted in the transformation of the hydrophobic 2-diazo-1, 2-naphthoquinone segment into the hydrophilic 3-indenecarboxylic acid. Furthermore, the ability of the micelles to release encapsulated drug was confirmed using hydrophobic model drug coumarin 102-loaded nanocarriers (Chen et al., 2011).

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For such biomedical applications, the choice of the wavelength utilized to activate the photoreactions is critical. For example, the UV irradiation utilized in the previously described studies to trigger either irreversible or reversible photo-induced reactions is unsuitable for biomedical applications owing to the damage caused to healthy tissues along with the limitation of tissue penetration, which is probably due to the strong scattering by soft tissues (Zhou, Z. et al., 2018). However, the use of near infra-red (NIR) light with wavelengths ranging from 700 to 1000 nm represents a solution that allows deeper penetration and less scattering by soft tissues. In addition, no significant damage to cells or tissues in the area of application was observed when NIR light was used. In particular, Xiang et al. (2018) used upconversion nanoparticles (UCNPs) in preparing NIR light-responsive drug release nanocarriers. The UCNPs were coated with an amphiphilic diblock copolymer, of which the core comprised hydrophobic UV-responsive poly(4,5-dimethoxy-2-nitrobenzyl methacrylate) (PNB) and the shell consisted of hydrophilic poly(methoxy polyethylene glycol monomethacrylate) (POEG). The study showed that upon 980 nm NIR light irradiation, the PNB core absorbed the UV light emitted by a single UCNP, which caused cleavage of the *o*-nitrobenzyl groups. Consequently, the hydrophilicity of the PNB core dramatically increased owing to the formation of carboxylic acid. This change in polarity shifted the hydrophilic-hydrophobic balance, which led to disassembly of the micelle and thus releases the encapsulated hydrophobic drug.

Li et al. (2017) described a biocompatible smart drug delivery system using doxorubicin anchored to hollow magnetic Prussian blue nanoparticles; resulting in HMNP-PB@Pent@DOX. As per the authors, the system shows concentration reliant on high thermogenesis (>50 °C) in near-infrared (NIR) laser irradiation. The method was found capable to release the drug by simply NIR laser irradiation. Furthermore, the authors claimed effective chemo-photothermal combined tumor therapy in vivo with 808 nm laser irradiation for 5 min at 1.2 W cm^{-2}. The method was better in inhibiting tumor in comparing with chemotherapy or photothermal therapy alone. The system was also found biocompatible with respect to the mortality rate. Chen et al. (2017) studied the effect of NIR on triggered molecule release and chemo-photothermal therapy. They developed Au/Fe_3O_4@polymer nanoparticles and tested their loading capacity for doxorubicin. These were tested on HT-29 tumor-bearing nude mice with less bodyweight loss and found with different drug release at different NIR irradiations. Furthermore, synchrotron-based FTIR imaging and confocal imaging indicated the direct reflection of the effective photo-chemotherapy impacting MCF7/ADR, MCF7 and HT-29 cells after the near infrared radiation triggered DOX discharge. Zhong and co-workers (Zhong et al., 2014) developed cRGD directed, NIR responsive and robust AuNR/PEG–PCL hybrid nanoparticles (cRGD-HNs). The authors used them for applying chemotherapy of human glioma xenografts in mice. cRGD-HNs had outstanding colloidal stability. The *in vitro* release studies indicated that drug release from doxorubicin anchored cRGD-HNs (cRGD-HN-DOX) was small in normal physiological conditions but significantly increased using NIR irradiation (low power density of 0.2 W/cm^2). MTT assays indicated that the antitumor activity of cRGD-HN-doxorubicin in αvβ3 integrin over expressed human glioblastoma U87MG cells was highly increased by slight NIR irradiation, that was remarkably more effective than non-targeting HN- doxorubicin complement in the similar conditions and was equivalent or better to free doxorubicin; assisting receptor facilitated endocytosis mechanism. In vivo pharmacokinetics assays indicated that cRGD-HN-doxorubicin was much longer circulation time than free doxorubicin. In vivo imaging and biodistribution, assays indicated that cRGD-HN-DOX might be actively targeted human U87MG glioma xenograft in nude mice. As per the authors, the therapeutic assays in human U87MG glioma xenografts showed that cRGD-HN-DOX in mixture with NIR irradiation totally reduced tumor growth and showed low side effects. The authors claimed their work as an attractive platform for cancer chemotherapy in vivo.

7. Dual-responsive polymeric nanocarriers

Over the past several years stimuli-responsive polymeric nanocarriers have attracted considerable attention in biomedical fields for controlled drug delivery. They have been increasingly constructed to encapsulate the therapeutic agent while simultaneously ensuring specific delivery to the desired sites and/or at the right time. In an attempt to further increase the response rate and the complete achievement of drug release into the targeted sites, dual-responsive nanocarriers that respond to a combination of two signals, i.e. pH/temperature, pH/redox, and photo/ temperature, have recently been developed (Hu et al., 2016; Vasantha et al., 2018; Zhang and Hadjichristidis, 2018; Zhou, Z. et al., 2018).

For example, in a study carried out by Hu et al. (2016) a pH/redox-responsive solid tumor-specific nanocarrier was described. The dual-responsive nanocarrier was prepared by inserting a redox-responsive disulfide bond between poly(amidoamine) dendrimers (PAMAM) and PEG segments, which were used to load the anti-cancer drug DOX, increase circulation time, and control intracellular drug release. The drug was loaded into the core of the micelles to obtain the PAMAM-SS-PEG/DOX drug delivery system (PSSP/DOX). The *in vitro* drug release investigations clearly showed a redox and pH dual-responsive drug release profile that increased as the degree of PEGylation increased. The in vivo investigation of the drug delivery system in B16 tumor-bearing mice revealed that PSSP/DOX could dramatically improve the antitumor efficacy (Hu et al., 2016). These well-defined and dual-responsive nanocarriers have therefore been demonstrated to constitute a promising platform for controlled drug release and enhanced solid tumor therapy.

Combinations of several stimuli have also been exploited to construct multi-responsive nanocarriers with various signals. In this regard, Xie et al. (2016) constructed a triple-stimuli-responsive nanocarrier based on graft copolymer assembly. The amphiphilic polycarbonate was comprised of temperature-responsive tetraethylene glycolyl poly (trimethylene carbonate) as a substrate and light-responsive poly(2-nitrobenzyl methacrylate) as a side chain attached by a redox-responsive disulfide linker, which was self-assembled in aqueous medium as a nanocarrier for the hydrophobic drug Nile Red. The drug release studies revealed a good response to temperature, reducing agent, and light (Xie et al., 2016). Recently, Zhang et al. (2018) designed a pH, reduction, and temperature triple-stimuli-responsive tetrablock copolymer as a nanocarrier for DOX. In aqueous solution, the nanocarriers based on the tetrablock copolymer poly(polyethylene glycol methacrylate)–poly[2-(dimethylamino) ethyl methacrylate]–poly(*N*-isopropylacrylamide)–poly(methacrylic acid) self-assembled into non-crosslinked micelles. The study showed that the rate of DOX release was facilitated by single or combined stimulation. Furthermore, loading of DOX led to micelles that exhibited increased inhibition of HepG2 cell proliferation. Moreover, as such dual- or multi-responsive drug delivery systems exhibit excellent circulation time and control of intracellular drug release, it is expected that the next generation of stimuli-responsive drug nanocarriers will employ a combination of two or more stimuli in a single nanocarrier. However, the complexity of such nanocarriers increases dramatically and work is still required to demonstrate the clinical efficacy of these systems. The different types of polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy are summarized in Table 1.

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Table 1
The different types of polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy.

S. No.	Polymeric nanocarriers	Drugs loaded	Stimuli responses	Types of studies	Refs.
1.	Poly(ethylene glycol)-poly(aspartate hydrazone adriamycin)	Adriamycin	pH	In vitro and in vivo studies	Bae, et al. (2005)
2.	Mono-2,4,6-trimethoxybenzylidene-pentaerythritol carbonate (TMBPEC, 2a) & mono-4-methoxybenzylidene-pentaerythritol carbonate	Paclitaxel and doxorubicin	pH	*in vitro*	Chen et al. (2009)
3.	Stearoyl-PEG-polySDM copolymer	Gemcitabine	pH	MCF-7 tumour cells	Bersani et al. (2014)
4.	Poly(ethylene glycol) (PEG) and biodegradable polycarbonate	Doxorubicin	pH	Nude mice bearing BT-474 xenografts	Teo et al. (2017)
5.	Four-arm star copolymer [poly(ε-caprolactone)-b-poly(poly(ethylene glycol) methyl ether methacrylate-co-p-(2-methacryloxyethoxy) benzaldehyde)]$_4$ [4-AS-PCL-P(PEGMA-co-MAEBA)]	Camptothecin	pH	HepG2 tumor cells	Xiong et al. (2017)
6.	Hydrophilic poly(ethylene glycol) (PEG) and hydrophobic poly(γ-benzyl L-glutamate) (PBLG),	Doxorubicin	pH	SCC7 cancer cells	Thambi et al. (2011)
7.	Polypeptide-based nanorods comprising anionic methoxypolyethylene glycol-poly	Doxorubicin	pH	A549 cells	Zhang et al. (2016)
8.	Poly (ethylene glycol)-b-poly (2-(diisopropylamino) ethyl methacrylate) block copolymer	Doxorubicin	pH	In vitro	Xu et al. (2017)
9.	Amphiphilic block polymer	Doxorubicin	pH	In vitro	Xu, J. et al. (2018)
10.	Hyaluronic acid-hydrazone linkage-doxorubicin	Doxorubicin	pH	In vitro	Liao et al. (2018)
11.	H7K(R_2)$_2$-modified-sensitive liposomes	Doxorubicin	pH	Glioma tumor cells	Zhao et al. (2016)
12.	Poly[2-(2-methoxyethoxy) ethyl methacrylate-co-oligo (ethylene glycol) methacrylate]-b-poly(L-lactide)-b-poly[2-(2-methoxyethoxy) ethyl methacrylate-co-oligo(ethylene glycol) methacrylate	Curcumin	Temp.	In vitro	Hu et al. (2015)
13.	Polymer polyTEGDA-b-poly-(NIPAM-co-NMA), with poly tetra(ethylene glycol) diacrylate as the hydrophobic core and poly(N-isopropylacrylamide-co-N-methylolacrylamide) (poly(NIPAM-co-NMA)) as the hydrophilic arms	Doxorubicin	Temp.	Ovarian carcinoma SKOV3 cells	Xu, N. et al. (2018)
14.	Glutathione-responsive polymeric	Doxorubicin	Redox potential	A549 cells	Duan et al. (2018)
15.	Core-cross linked polymer	Doxorubicin	Redox potential	HepG2 cells	Xia et al. (2018)
16.	Folate-conjugated poly(ethylene glycol)-b-copolycarbonates (FA-PEG-b-P(MAC-co-DTC)) and methoxy poly(ethylene glycol)-b-copolycarbonates (mPEG-b-P (MAC-co-DTC)	Doxorubicin	Redox potential	In vitro	Lv et al. (2018)
17.	Poly(ethylene glycol)-block-poly(2-(methacryloyloxy)ethyl 5-(1,2-dithiolan-3-yl) pentanoate) diblock copolymers	Doxorubicin	Redox potential	In vitro	Maiti et al. (2018)
18.	Hyperbranched poly(2-((2-(acryloyloxy)ethyl)disulfanyl)ethyl 4-cyano-4-(((propylthio)carbonothioyl)-thio)-pentanoate-co-poly(ethylene glycol) methacrylate) (HPAEG)	Doxorubicin	Redox potential	In vitro	Zhuang et al. (2016)
19.	PEG2000-peptide-PTX	Paclitaxel	Enzyme	In vitro	Zhu et al. (2013)
20.	N-(2-hydroxypropyl)-methacrylamide	Doxorubicin	Enzyme	DU-145 cells	Peng and Kopeček (2015)
21.	Poly(ethylene glycol)-b-poly(L-tyrosine) block copolymer	Doxorubicin	Enzyme	RAW 264.7 cells and HCT-116 human colorectal cancer cells	Gu et al. (2018)
22.	Poly(ethylene glycol)-b-poly(ethanedithiol-alt-nitrobenzyl)-b-poly(ethylene glycol)	Doxorubicin	Light	A549 cells	Jin et al. (2014)
23.	Poly(ethylene oxide)-block-poly[(oligoethylene glycol) methacrylate-random-(2-diazo-1,2-naphthoquinone oligoethylene glycol) methacrylate	Coumarin	Light	In vitro	Chen et al. (2011)
24.	Hollow magnetic Prussian blue nanoparticles	Doxorubicin	Light	In vitro	Li et al. (2017)
25.	Au/Fe_3O_4@polymer	Doxorubicin	Light	In vitro	Chen et al. (2017
26.	Gelatin/poly(acrylic acid)	Cisplatin	Light	In vitro	Ding et al. (2012)
27.	Hollow mesoporous silica (HMS) nanoparticles modified with spiropyran-containing light-responsive copolymer (PRMS-FA)	Spiropyran	Light	In vitro	Xing et al. (2014)
28.	Poly(amidoamine) dendrimers (PAMAM) and PEG segments	Doxorubicin	pH/redox	B16 tumor-bearing mice	Hu et al. (2016)
29.	Tetraethylene glycolyl poly (trimethylene carbonate) as a substrate and light-responsive poly(2-nitrobenzyl methacrylate) as a side chain	Nile Red	Temp./light	In vitro	Xie et al. (2016)
30.	Tetrablock copolymer poly(polyethylene glycol methacrylate)–poly[2-(dimethylamino) ethyl methacrylate]–poly(*N*-isopropylacrylamide)–poly (methacrylic acid) self-assembled into non-crosslinked micelles	Doxorubicin	pH/temp.	HepG2 cell	Zhang et al. (2018)

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8. Future perspectives

The targeted chemotherapy in treating cancer is attracting academicians, researchers, oncologist and industrial persons for a long time (Ali, 2011; Ali et al., 2013a,b). Of course, this is one of the alternatives for exact, safe and targeted treatment to the cancerous cells. For this purpose, some drug carriers are utilized and among them, nanocarries are gaining importance due to their unique feature. Amongst various sorts of the nanocarries, the polymeric nanocarriers are considered as the best ones due to their good drug loading capacities, biodegradability, and stimuli-responsive control. Many papers are available on polymeric nanocarriers in cancer chemotherapy but only a few articles describing controlled and remote drugs release via stimuli-responsive control. It was also observed that much work has not been carried out. There are certain challenges and issues, which include their preparation, efficacy, toxicity and bioavailability. There is a great need to explore the efficient ways of anchoring anticancer drugs on stimuli-responsive polymeric nanocarriers. The hydrophobic drugs and contrast agents can easily get anchored onto the micellar core by covalent bonding and hydrophobic interactions. The toxicity linked to these nano-formulations cannot be overlooked and less information is existing on the toxicity issue in the human body (Luk and Zhang, 2014). The tissue penetration and bioavailability of the drugs loaded polymers are other concerns. There are only a few studies dealing with the bioavailability of the anchored drugs, which need further studies to advance the bioavailability of the drug.

For the bright future of targeting chemotherapy, the above mentioned challenges are to be addressed and resolved. The advancements in stimuli-responsive polymeric nanocarriers will have to resolve/address these issues i.e. loading capacity, tissue penetration, biodegradability, controlled drug release and bioavailability. It is significant to cite that stimuli-responsive polymeric nanocarriers are not fully developed and need more advancements. The compound structures of these polymeric are hard to take care of in preparation. The imaging plans require to be enhanced to evade patients' toxicity. Besides, it is important to change the features of polymers to augment load-ability, bioavailability, biodegradability, and biocompatibility. From the discussion in this article, it was realized that the different types of changes in cancerous cells are exploited to release drugs under control but none of them are perfect. It means more researches are needed to achieve the perfectness in the targeted and controlled drug release. It will be great if we can modify/change the polymeric nanocarriers, that may react under different stimuli (pH, temperature, redox potential, enzyme, light, and radiation) simultaneously - multi-responsive polymeric nanocarriers. If we are success to prepare such nanocarriers, certainly, these may be perfect ones for excellent targeting drug release and bioavailability without any side effect or toxicity. This will lead to better therapeutic outcomes, no toxicity with the economy.

9. Conclusions

In this review, it was focused on the most recent advances in the development of stimuli-responsive nanocarriers for drug delivery in cancer therapy. These smart drug delivery systems respond to the distinct changes in cancer cells, such as changes in pH gradient and elevated secretion of certain enzymes, rather than the conditions in normal cells. Targeting tumors with stimuli-responsive nanocarriers could not only increase the therapeutic benefit and minimize associated toxicity, but could also enhance the curative effect by specifically releasing the anti-cancer drug in a powerful precise mode, both temporally and spatially. The different approaches adopted to incorporate stimuli responsive elements within the polymeric nanocarriers were discussed, with a particular focus on polymeric materials with stimuli-responsive mechanisms in response to pH, redox potential, enzymes, temperature, and light.

Despite the tremendous progress that has been made regarding the engineering of new stimuli-responsive materials, several challenges still remain to be addressed with respect to nanomedicine applications. For example, their biodegradability and biocompatibility profiles should be critically investigated prior to utilization in human clinical trials. Many of these systems have only been reported as an *in vitro* proof-of-concept and follow-up work in *vivo* preclinical models has been described for only a few. However, the translation of these stimuli-responsive delivery systems from the bench to the bedside might be facilitated, to some extent, if the regulatory requirements for human clinical trials are considered in light of the key features that render a biopolymer suitable for biomedical application, such as biocompatibility, biodegradability, high drug loading capability, programmable release, excellent in vivo stability, non-cytotoxicity, and ability to support effective targeting. Given the ongoing developments in the field of bionanotechnology along with the wide knowledge accumulated over recent years, it is convinced that the collaborative efforts of chemists, biologists, and medicinal and pharmaceutical scientists will revolutionize the design of responsive polymeric materials for cancer therapy to significantly improve both the quality and duration of the lives of patients with cancer.

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Declaration of Competing Interest

The author declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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