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REVIEW

pH-sensitive polymeric nanocarriers for antitumor biotherapeutic molecules targeting delivery

Jiayi Qin[1] · Yangbo Zhu[1] · Dongsheng Zheng[1] · Qingwei Zhao[1]

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Abstract

pH-sensitive smart polymeric nanocarriers have been under development in the field of biomedicine due to permeabilization the physiological barriers readily to address the limitation of conventional chemotherapeutics delivery systems of low intracellular transport and targeting efficiency. Where traditional polymers kept stable under physiological neutral or acidic conditions, pH-sensitive polymeric nanocarriers underwent rapid degradation with a labile group in tumor acidic environment (around 5.0–6.0), allowing these biomaterials to achieve controlled drug release, drug pharmacokinetics improvement and antitumor biotherapeutic molecules efficiency enhancement compared with traditional polymers. This review mainly concentrated on properties of pH-sensitive polymers for biomedical purposes to construct the smart drug delivery system based on acid liable linkers which were categorized into pH-sensitive polymeric prodrugs composed of antitumor drugs (doxorubicin and paclitaxel) bounded to the polymer via acid liable linkers and pH-sensitive copolymeric nanocarriers prepared by block copolymers containing polymer blocks linked with acid-cleavable groups. Besides, advanced platforms in biomedicine for special biotherapeutic molecules delivery were reviewed in the article. Furthermore, several acid-sensitive linkages were reviewed to study the mechanism of the controlled pH-responsive drug delivery, such as hydrazone, acetal, *cis*-aconityl linker and β-thioether ester, as well as improvement of drug pharmacokinetics.

Keywords pH-sensitive polymeric nanocarrier · Acid-liable linkage · Antitumor biotherapeutic molecules · Targeting delivery · Pharmacokinetics

Introduction

Cancer is a leading cause of death worldwide remaining much challenge [1]; despite the availability of chemotherapy in the conventional treatment of various tumors [2], the major limitation to the clinical is the inefficient cellular uptake, serious side effects of antitumor drugs of low selectivity [3], and ascribed the obstacles from the site of administration to the desirable targeting sites. In general, the tumor microenvironment is a complex structure comprising of tumor cells, less well organized blood vessels, cytokines and altered extracellular matrix substantially different from normal tissues [4]. These barriers such as blood perfusion, tumor lymphatic drainage, tumor cell density, intratumoral pressure gradient and extracellular matrix hinder drug penetration into tumor tissues, lead to poor distribution and low chemotherapeutic efficacy. After entering the tumor cells, the intracellular components also challenge the drug efficiency; the bioavailability was influenced by the drug internalization across the tumor walls and releases from endosomes/lysosomes [5].

Various strategies were explored to circumvent the multiple biological barriers and improve the delivery efficiency of nanomedicines, such as passive and active targeting delivery [6, 7]. Bio-design polymeric nanocarriers have not only proved beneficial to increase their localization in specific tumor cells, but also have found their promising application in the rapid growth of biomedicine from the diagnosis to treatment of many kinds of tumors [8–12]. Currently, it is found that these nanocarriers can passively target tumor by the enhanced permeation and retention (EPR) effect [13], which is the prerequisite for intracellular delivery. The longer blood circulation time and higher tumor cellular uptake are beneficial for enhancing passive targeting. However, the demands in terms of size and surface of nanocarriers for

✉ Qingwei Zhao
qwzhao@zju.edu.cn

[1] The First Affiliated Hospital, Zhejiang University School of Medicine, #79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China

the optimal targeting delivery efficiency are even contradictory. For instance, larger sizes and negatively charged surface can favor blood circulation and thus facilitate passive tumor targeting, but actively prevent cellular membrane transport, leading to poor tumor inhibition [14]. Some studies have revealed that the "PEG dilemma" phenomenon of nanocarriers prevents tumor cellular uptake [15]. Meanwhile, approaches aiming at improving the therapeutics delivery to intended targets include the lipid membrane fusion of liposomes [16], actively nanoparticles conjugating targeting ligands etc. [17]. As for the active targeted delivery systems, despite expected results in some studies, most ligand-modified nanocarriers often cause non-selective interactions between tumor cells and normal tissues [18]. Nevertheless, the receptors heterogeneous expression of different tumors can further prevent the extravasated nanocarriers into tumor cells. Therefore, there are some challenges for the passively and actively targeted delivery systems. Undoubtedly, these normal systems suffer from various obstacles which definitely compromise the targeting efficiency and therapeutic effects.

In order to significantly optimize antitumor efficacy of chemotherapeutics while minimizing their systemic toxicity, smart polymeric nanocarriers have provided an attractable strategy to realize the "on-demand" site specific antitumor drug targeting delivery based on the tumor unique environment. Apart from the advantages of normal biomaterial such as hydrophobicity, these smart polymers have capability of responding to external or internal stimulus, such as temperature, pH, light, enzymatic reactions or redox, with a sharp change yielding the material with new desired properties to circumvent drug disappointed low efficacy [19–21].

It has been long recognized that the interstitial pH of tumors is known to be more acidic than the pH 7.4 in normal tissues and blood and intracellular endosomal and lysosomal pH is notably lower [22, 23]. pH-responsive drug delivery systems (DDS) have been extensively applied as obvious pH changes occur within different tissues and cellular compartments [24–26]. Accordingly, various materials have been functionalized to design pH-sensitive delivery systems [27–29]. After a systemic administration, cancer therapeutics undergo elimination, e.g., enzymatic degradation in blood, hepatic metabolism and renal excretion, the pharmacokinetic processes and physicochemical interactions of free drugs preclude the targeting and the efficient intracellular transport into particular cells in a conventional drug delivery. On the contrary, such intellectual systems have adequate stability during long circulation but activate drug accumulation and release in tumor sites through dissemble, collapse or degradation upon the presence of expected acidic pH [30]. Thus, pH-sensitive nanocarriers have been extensively applied to alter the drug pharmacokinetics to enhance antitumor efficacy thanks to their unique advantages [31, 32].

Owing to the special properties of functional pH-sensitive nanomaterials, multifunctional systems could be constructed to improve biomedical applications, including drug delivery and clinical therapy. Here, we introduced the mechanism of pH-sensitive nanocarriers and reviewed recent progress on application of pH-sensitive drug targeting delivery systems based on the cleavage of acid liable bonds including hydrazone, acetal bond, *cis*-aconityl linker, ortho ester, β-thiopropionate groups, etc., in antitumor targeting treatment. Besides, advanced delivery platforms in biomedical technologies were reviewed for special antitumor biotherapeutic molecules targeted therapy. Furthermore, the behavior of these pH-responsive polymers underwent in response to acidic pH and the pharmacokinetics of pH-sensitive nanocarriers was also discussed in this review.

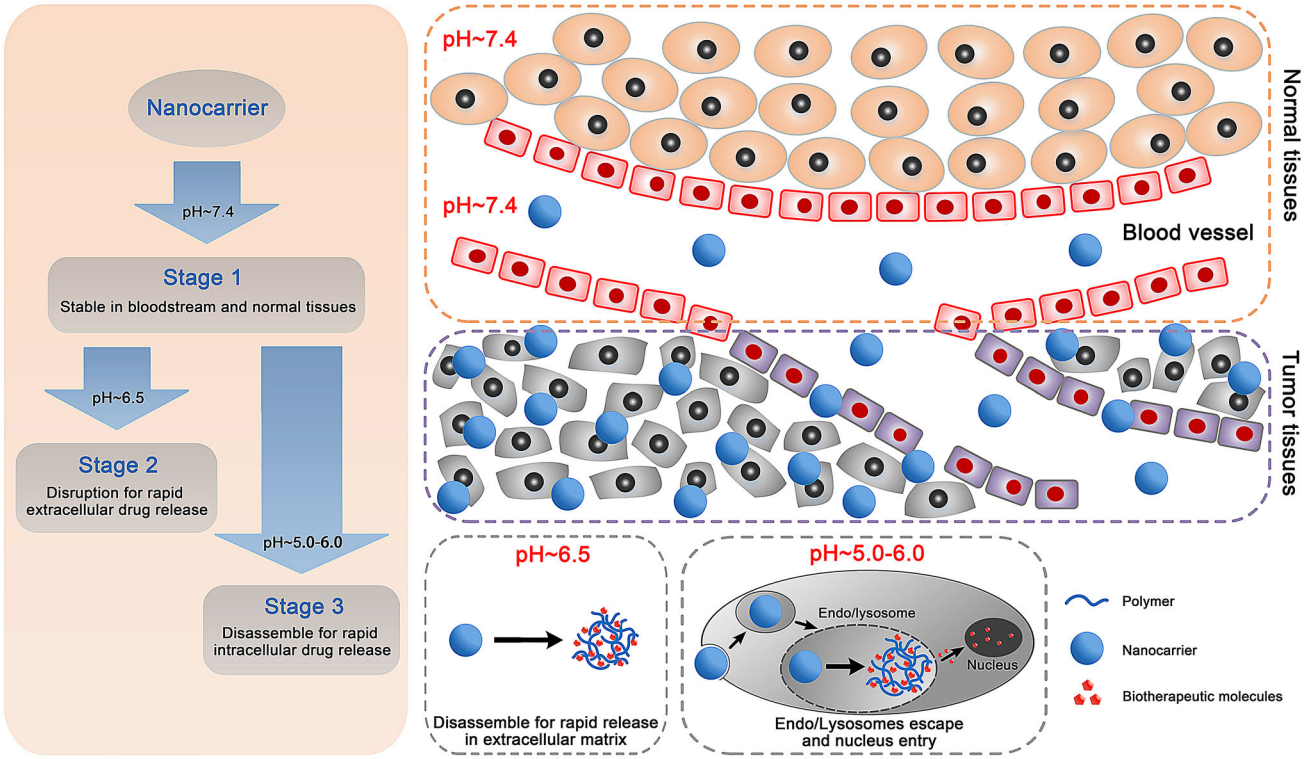
Mechanism of pH-sensitive polymeric nanocarriers for antitumor biotherapeutic molecules targeting delivery

Environmental stimuli-responsive delivery systems are formulated with "load-and-release" smart units that in respond to external stimuli (light, temperature, ultrasound waves, magnetic or electric field, etc.) and internal stimuli (pH, redox, enzymes, reactive oxygen species, etc.) and thereby improved drug therapeutic efficacies [33–35]. These smart delivery systems are specialized delivery vehicles that evolve from the need for drug target and better control of drug release.

According to Warburg Effect, malignant cells require enough oxygen to efficiently survive reliant on increased anaerobic glycolysis instead of the Krebs cycle causing lactic acid accumulation and hence resulting in lowered pHe [36, 37]. It is well recognized that the tumor pHe is lower than the physiological pH (pH 7.4) [38] and is around 5.0–6.0 in lysosomes and endosomes [39]. Hence, pH-sensitive nanocarriers (micelles, nanogels, polymer–drug conjugates, etc.) have been developed extensively for target cancer cells based on the lowered pHe [40–42].

The idea of pH-sensitive drug delivery was introduced in 1980 [43]. In physiological environment, the nanocarriers are characterized by excellent stability but prone to rapidly dissemble, collapse or degradation in sharp response to an acidic pH stimulus. Later on, it was reported that altered pH in tumor extracellular or intracellular environments presented advantages such as accumulation in cancer cells via either passive or active targeting, following activation in the tumor site or inside the tumor cells and result in efficient cancer therapy in the design of pH-responsive nanocarriers [44, 45].

Functionalized materials assembled for pH-responsive drug delivery systems with desired properties promote great potential in cancer therapy. With respect to materials options



Scheme 1 The mechanism of endogenous acidic pH-sensitive polymeric nanocarriers for antitumor biotherapeutic molecules targeting delivery. Stage 1: stable in bloodstream and normal tissues, pH ~ 7.4 for bloodstream and normal tissues. Stage 2: high accumulation at tumor tissues, pH-sensitive nanocarriers disruption and triggering drug release in the tumor's extracellular matrix, pH ~ 6.5 for tumor extra-environment. Stage 3: Stable at tumor extra-environment, tumor cellular uptake and subsequent pH-sensitive intracellular drug release, pH ~ 5.5 for endosome, pH ~ 5.0 for lysosome

for pH-sensitive nanocarriers, smart drug delivery systems are those with versatile chemical structures allowing them to bear stimuli-responsive groups to readily modulate drug release triggered by tumor acidic pH. As illustrated in Scheme 1 [46–50], the structures of nanocarriers are kept stable in blood pH 7.4, while sensitive at the tumor extracellular environment with pH of 6.0–7.2. This pH difference could then be used to trigger drug release in the tumor's extracellular matrix. Once being internalized, the drug carriers could be disassembled as pH dropped from 7.4 to endosomal or lysosomal 5.0–6.0, promoting the nanocarriers escape into the cytoplasm and triggering drug release. Consequently, it controls cargo drugs to release by degradation-mediated nanocarrier activation in the acidic conditions. Degradation-mediated pH of some polymers in water is summarized in Table 1.

Figure 1 depicts pH-sensitive drug release from nanocarriers in response to tumor extracellular or intracellular environments. The PEG surface layer was detached from the tumor extracellular microenvironment pH-labile linkage-bridged block copolymer to facilitate cellular uptake and the siRNA rapidly release, resulting in the enhanced therapeutic effect [59]. The acid-triggered rapid drug release can be achieved outside or inside tumor cells by using polymers bearing pH-sensitive components. The intracellular delivery of antitumor drugs by conjugating DOX onto hydroxyethyl starch (HES) with a pH-sensitive hydrazone (Hyd) bond potentiated the effect to reduce the drug fast clearance from the blood system and severe systemic toxicity [60].

Currently, most work in the area focuses on enhanced cellular internalization and rapid intracellular drug release in designing pH-sensitive nanocarriers of delivery cancer drugs [61]. These nanocarriers provide an opportunity to alter drug pharmacokinetics and biodistribution, facilitate drug accumulation in tumor cells and then uptake and trigger drug release at the desirable site. This is particularly useful to improve targeting selectivity, enhance drug efficacy, reduce the side effect of chemotherapy and increase patients' compliance.

pH-sensitive drug targeting DDS based on the cleavage of acid-liable bond

Accordingly, plenty of efforts have been made towards the effective design of pH-sensitive drug delivery system. The

Table 1 The degradation-mediated pH of polymers in aqueous solution

Polymer acid-sensitive bonds	Polymer nanocarriers	Polymer degradation-mediated pH	References
Hydrazone bond	Glyoxylic hydrazone linkages poly (ethylene glycol) hydrogels	pH 6.4	[51]
	Xanthan-poly (ethylene glycol) (PEG) hydrogels	pH 5.5	[52]
Cis-aconityl bond	DOX-loaded dendrimer-entrapped Au NPs	pH 6.0, 5.0	[53]
	folate/*cis*-aconityl-doxorubicin@polyethylenimine@cellulose nanocrystal	pH 5.5	[54]
Ester bond	DOX-loaded gelatin nanoparticles hybrid carboxymethyl chitosan hydrogels	pH 6.5, 5.0	[55]
	DOX-loaded PEG-block-poly (ortho ester urethane)-block-PEG micelles	pH 5.0	[56]
Acetal bond	Gemcitabine and hollow mesoporous organosilica nanoparticle complex	pH 6.5	[57]
	Indomethacin-grafted dextran copolymer micelles	pH 6.5, 5.0	[58]

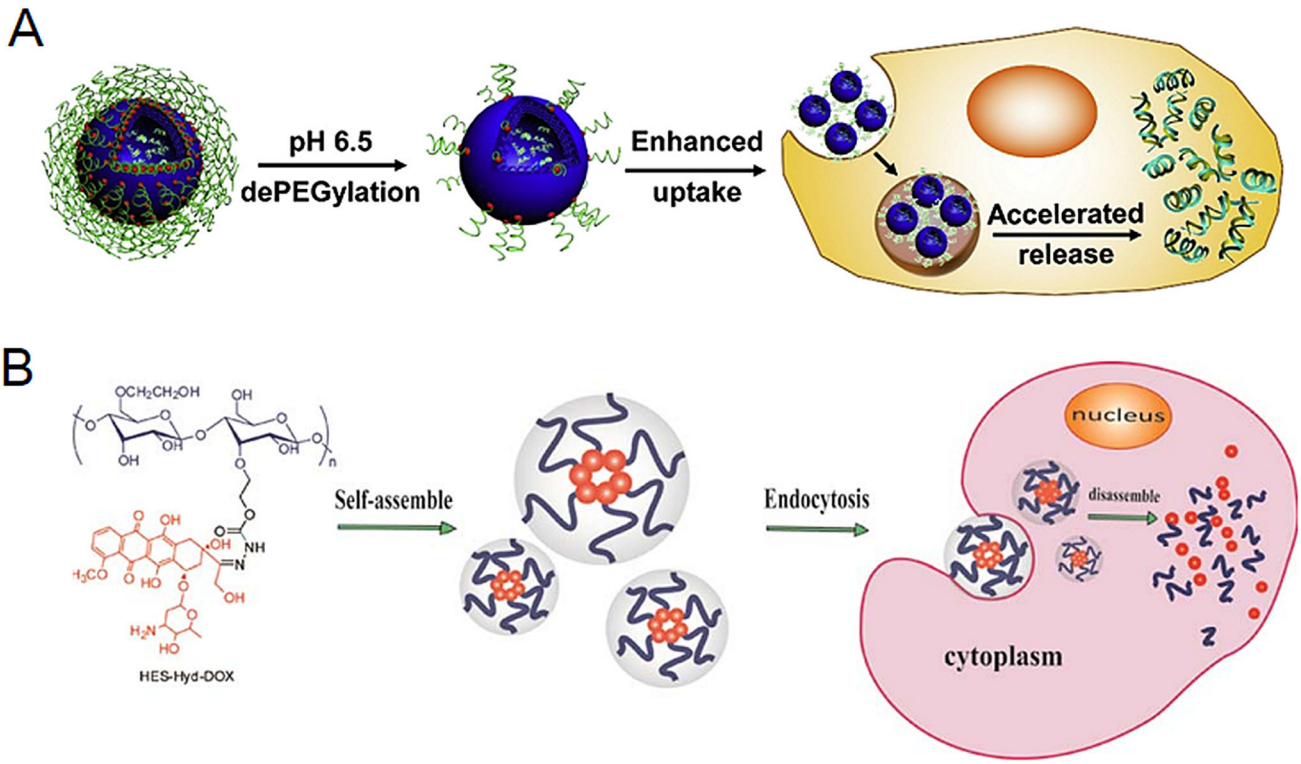


Fig. 1 pH-sensitive drug release from nanocarriers in response to tumor extracellular (**a**) or intracellular (**b**) environments. **a** Tumor pH-labile linkage bridged block copolymer enhancing tumor cell uptake by detaching the PEG layer at extracellular pH 6.5 tumor environment and accelerating intracellular siRNA release [59], Copyright 2016 Elsevier Ltd and **b** intracellular microenvironment triggered drug release of pH-sensitive HES-Hyd-DOX [60], Copyright 2015 Wiley Ltd

drug delivery systems are with pH-sensitive linker mainly including hydrazone bond, *cis*-aconityl linker, ester, acetal (Fig. 2) attached to the backbone or side chains of functional polymer by chemical reaction, and eventually preparation by pharmaceutical or other material science methods [62–65].

These polymers' smart pH-sensitive functions are based on the cleavage of acid-liable bonds. Under normal physiological conditions, the materials are insensitive to maintain steady state, once reaching the acidic tumor microenvironment (pH value decreased), their structure changes in response to the decreased pH values whose cleavage of acid-sensitive linkers triggers either the drug release or the PEG detachment, and thereby improve the therapeutic effect. The

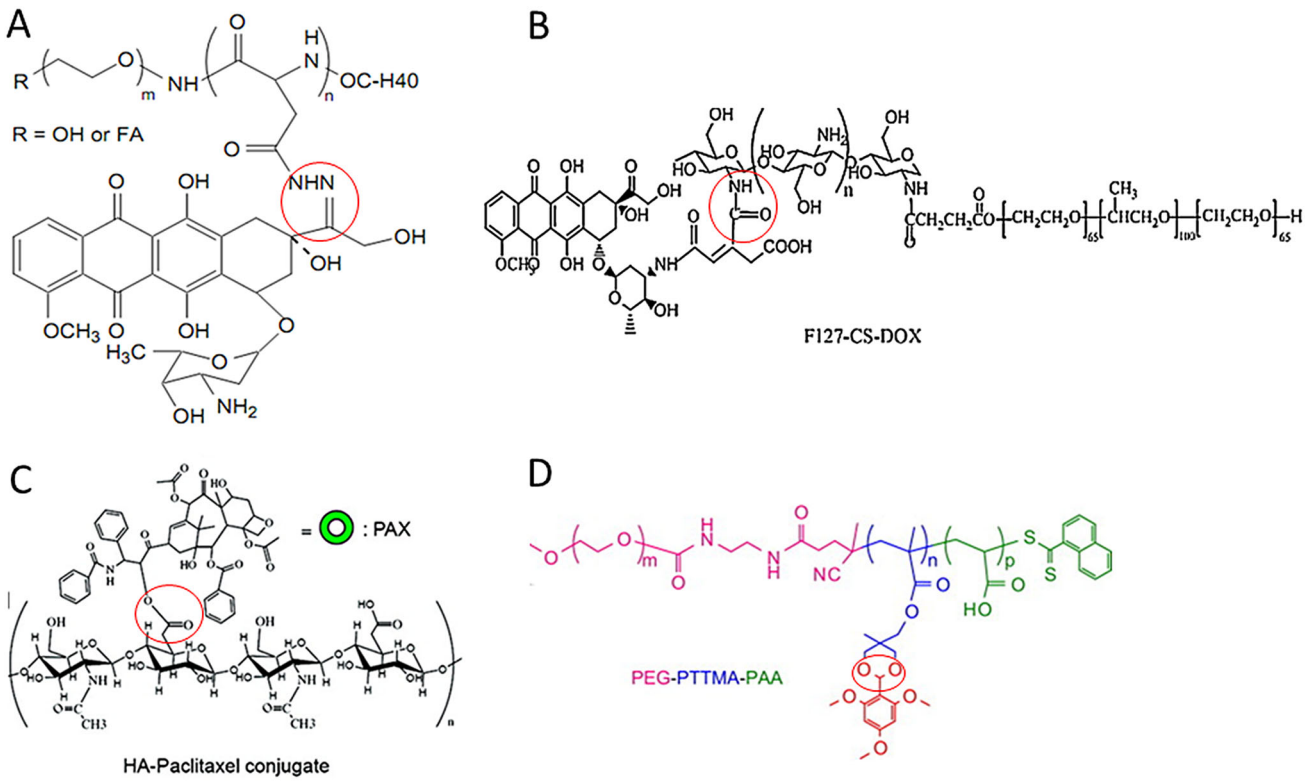


Fig. 2 **a** FA-conjugated amphiphilic hyperbranched block copolymers via a hydrazone linkage [62], Copyright 2009 Elsevier Ltd; **b** Pluronic F127-chitosan-doxorubicin through amide bond between the *cis*-aconitic anhydride modified doxorubicin and Pluronic F127-chitosan [63], Copyright 2016 Elsevier Ltd; **c** Hyaluronic acid – paclitaxel conjugation through ester bond [64], Copyright 2008 American Chemical Society; **d** pH-sensitive asymmetric poly(ethylene glycol)-*b*-poly(trimethoxy benzylidene tris(hydroxymethyl)ethane methacrylate)-*b*-poly(acrylic acid) (PEG-PTTMA-PAA) triblock copolymers based on the pH-sensitive degradation of acetal for triggering DOX·HCl release [65], Copyright 2012 Elsevier Ltd. The acid-labile moieties in chemical structures of these examples were circled

recent progress on the design of pH-sensitive develop systems based on acid-liable bonds is discussed below.

pH-sensitive polymeric prodrugs

These pH-sensitive drug–polymer conjugates were composed of antitumor drugs bounded to the polymer via acid cleavable linkers, such as hydrazone bond, *cis*-aconityl bond, acetal, ester, inactive until acidly activated in vivo into active drugs once they have reached intended target site [66–69]. The prodrug strategy provides many antitumor drugs the promising clinical applications in cancer targeting therapy.

Doxorubicin (DOX), also known as Adriamycin (ADR), a potent chemotherapeutic drug showing a high activity against a range of human tumors is plagued with extra- and intra-cellular barriers, such as the extracellular instability and intracellular DOX release dilemma [70, 71]. In recent years, much effort has been directed to the development of pH-sensitive prodrugs to improve antitumor activity in responsive to tumor acidic pH [72–75]. The group of Li developed a drug delivery system in which DOX was conjugated onto pullulan molecule via pH-responsive hydrazone bond and Pu-DOX could easily self-aggregate to form nanoparticles with core–shell structure as illustrated in Fig. 3A. Compared with the control group, DOX was rapidly released from Pu-DOX nanoparticles in the acidic environment at pH = 5.0 (endosome/lysosome), diffused into cell nuclei due to its strong affinity to nucleic acid, inhibited the cell proliferation and accelerated the cell apoptosis(Fig. 3b, c), which might provide an important clinical implication for targeted hepatic carcinoma therapy with high efficiency [73].

DOX was usually loaded onto nanocarrier via pH-sensitive hydrazone bond forming between amine as well as hydrazine groups of nanocarriers and carbonyl at C-13 position of DOX [66, 72, 76]. Zhu et al. conjugated DOX onto hydroxyethyl starch through a pH-sensitive hydrazone bond. The conjugates could assemble to form nanoparticles whose scale size (about 100 nm) was suitable for entering into cancer cells and long circulation time in blood, while accelerating the DOX release once in intra-

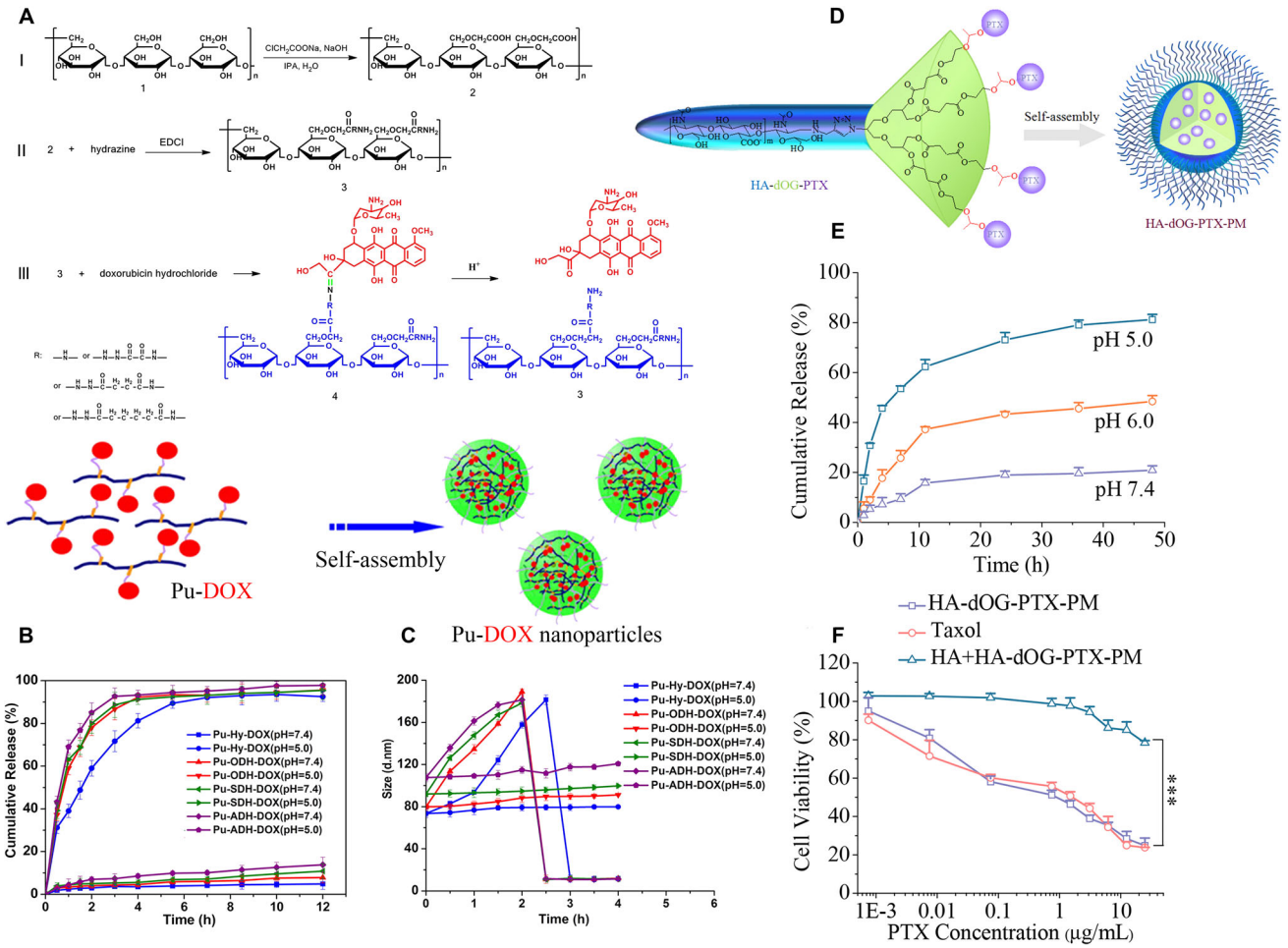


Fig. 3 Acid-labile chemical bonds used to conjugate drugs to nanocarriers. **a** Schematic illustrations of the structure of pullulan–doxorubicin conjugates and the formation of Pu-DOX nanoparticles through self-assembling; **b** In vitro drug release behavior of Pu-Hy-DOX, Pu-ODH-DOX, Pu-SDH-DOX and Pu-ADH-DOX nanoparticles at different pH values ($n = 3$); **c** Size change of Pu-Hy-DOX, Pu-ODH-DOX, Pu-SDH-DOX and Pu-ADH-DOX nanoparticles during the drug release process ($n = 3$) [73], Copyright 2015 American Chemical Society. **d** Endosomal pH-activatable HA-dOG-PTX-PM self-assembled in water for active CD44-targeted PTX delivery; **e** pH-dependent drug release from HA-dOG-PTX-PM at 37°C ($n = 3$); **f** The in vitro antitumor activity of HA-dOG-PTX-PM, Taxol was used as a control ($n = 6$), $^{***}p < 0.001$ [67], Copyright 2016 Elsevier Ltd

cellular lower pH value and providing a controlled and sustained release of DOX over a period of more than 3 days [60]. Similar acid-labile hydrazone linkage was conjugated DOX to 11-mercaptoundecyl phosphorylcholine. This phospholipid prodrug self-assembled into core–shell micelles and confirmed by the dynamic light scattering, showing that the average diameters of prodrug micelles were 136 nm and demonstrated smart intracellular microenvironment responsiveness and enhanced antitumor effect [77]. Multidrug resistance is one of the major obstacles in successful cancer treatment [78]. Combination chemotherapy has shown superior clinical therapeutic efficacy in avoiding chemoresistance owing to the peculiar synergistic effects and significantly improve the target selectivity. Cao et al. synthesized a reduction-sensitive dextran-ss-camptothecin (CPT) prodrug conjugated by a disulfide bond, and a pH-responsive dextran-hyd-doxorubicin prodrug linked with an acid-cleavable hydrazone group which could self-assembled into uniform particles and mixed in aqueous solution. Subsequently, synergistic drug was released from the prodrug micelles mixtures once the pH-sensitive hydrazone bond was broken under intracellular acidic conditions as well as the reduction of a disulfide linker generated the releasing native CPT molecules [79]. Li et al. have achieved significant antitumor efficiency and efficient suppressing of multidrug resistance of tumor cells through targeted delivery with combination of a pH-responsive DOX release by hydrazone bonds and a sensitizer [80].

Sometimes, the hydrolysis of hydrazone bond was too slow for PEG–DOX conjugate nanoparticles [81]. For DOX prodrug exploitation, some employed the amino group modification of DOX by forming an amide bond with an adjacent

carboxyl such as *cis*-aconitic anhydride-doxorubicin (CAD) conjugate coupled to the amino on the polymers [82, 83]. CAD conjugate was prepared by the amidation of amine group on DOX and anhydride moiety on *cis*-aconitic anhydride. *Cis*-aconityl linkers have been frequently employed to conjugate DOX due to its sensitivity to acidic tumor microenvironment. For instance, Song et al. reported a DOX prodrug formed from *cis*-aconitic anhydride-doxorubicin precursor coupled to the end amino group of PEG via amidation with the neuropilin-1 receptor targeting CendR peptide ligand Cys–Arg–Gly–Asp–Lys. Under neutral conditions, PEG–CAD prodrug was stable and drug release was greatly retarded. These nanoparticles accumulatively released around 55% DOX, while the control PEG–DOX nanoparticles coupled by succinic anhydride released only 12% DOX at pH 5.0, indicating that drug release was controlled by the cleavage of amide with neighboring double bond and carboxylic acid groups (*cis*-aconityl bond) between DOX and PEG. Consequently, the pH-sensitive *cis*-aconityl bond conjugated prodrug certainly enhanced undoubtedly endocytosis and cytotoxicity in HepG2, MCF-7 and MDA-MB-231 cells, but showed lower cytotoxicity in human cardiomyocyte H2C9 [84]. Ma et al. disclosed that a pH-sensitive polymeric micelle incorporated acid-liable *cis*-aconityl bonds between DOX and Pluronic F127-chitosan polymer exhibited acid-responsive release properties [63]. Wang et al. found that the intervening *cis*-aconityl linker in dextran-poly(ethylene imine) copolymers displayed pH-dependent progressive hydrolysis behavior [68]. The *cis*-aconityl bonds, while remained stable at neutral pH, accelerated hydrolysis under acidic lysosome condition, resulting in efficient delivery of DOX into tumor sites to suppressed MCF-7 cells effectively and reduce side effects. The pH value of *cis*-aconityl linker complete hydrolysis was less than 6, while endocytic vesicles during folate receptor-mediated endocytosis were at pH values around 6.6 [85]. Du et al. developed a pH-sensitive folate–bovine serum albumin (BSA)-*cis* aconitic anhydride-doxorubicin prodrug for tumor targeted delivery. DOX was conjugated to the BSA through an acid-labile *cis* aconitic anhydride bond modified by folic acid. Thus, modification of 10 folate in the prodrug compound could further decrease the endocytic vesicles pH value due to its free carboxyl group, which was adequate for rapid drug release, favoring for the targeted delivery of DOX to the acid tumor sites [86]. More importantly, acid-sensitive PEGylated DOX micelle could significantly inhibit the tumor growth toward H22-transplanted mouse models by tail vein injection [87]. The terminal hydroxyl group of mPEG and the carboxyl group in *cis*-aconitic anhydride-modified DOX polymer condensated and spontaneously self-assembled into micelles. The high antitumor efficacy was due to the prolonged blood circulation time, enhanced accumulation at the tumor site as well as selective acidity-triggered DOX release.

Besides hydrazone bonds and *cis*-aconityl linker, it is interesting to note that other pH-sensitive prodrug strategies have been exploited to improve DOX accumulation in the tumor, efficient uptake and intracellular drug release successful in cancer chemotherapy for DOX nanoscale delivery systems, such as a novel tetra-doxorubicin-tailed polyethylene glycol via benzoic-imine bond linkage [88]. To achieve good stability, long circulation and easy surface functionalities for targeting delivery of DOX to overcome multidrug resistance, DOX was chemically conjugated to the backbone of D-α-tocopherol polyethylene glycol 1000 succinate via acid-labile Schiff base linker, which was sufficiently stable at pH 7.4 but readily cleavable in an acidic environment [89]. Recently, a novel pH-sensitive linker based on a phosphoramidate scaffold that can be tuned to release amine-containing drug molecules, such as DOX, at various pH values was developed [90]. It should be noted that phosphoramidate hydrolysis was largely governed by the pKa of the leaving amine, while the proximity of the neighboring pyridine group or carboxylic acid could significantly attenuate the stability of the P–N bond to hydrolysis. Based on the data presented, candidate linkers would be selected for prodrug activation to control DOX release at various acidic tumor microenvironment.

Paclitaxel (PTX), an anti-mitotic chemotherapeutic agent, has also been demonstrated great potency against various cancers while hindered by poor aqueous solubility, and consequently has poor bioavailability and significant systemic toxicity. Moreover, the antitumor activity of PTX was generally low partly due to low tumor-targetability and/or slow intracellular drug release [91]. Recently, various pH-sensitive polymeric micelles or nanoparticles, self-assembled from amphiphilic polymer–PTX conjugates, were more efficient regarding high water solubility and aggressive anticancer activity and represented one of the most promising strategies to overcome the challenges of PTX conventional cancer therapy. These PTX prodrugs were most commonly synthesized by water-soluble synthetic polymeric conjugation at the 2′-hydroxy group of PTX via acid-liable linkages (e.g., ester bond, acetal bond) [92].

Hyaluronic acid (HA) and its derivatives have been popularly used in target-specific drug delivery vehicles for various pH-sensitive PTX prodrugs by utilizing reactive functional groups in HA such as carboxylic groups. Thus, hydroxyl groups of paclitaxel could directly conjugate to carboxylic groups of HA through an acid-cleavable ester linkage. After 3 h incubation of the HA paclitaxel conjugate at four different pH conditions (pH 1.0, 3.0, 5.0, 7.0), an intact paclitaxel peak appeared to a greater extent at more acidic pH by using reversed-phase HPLC [64]. Chen et al. reported an acidic cleaved ester bond conjugated drug–polymer by the copper-catalyzed azide–alkyne cycloaddition reaction between an azide-functional diblock

copolymer and an alkyne-functional paclitaxel. Significant PTX release acceleration was actuated at pH 5.5 due to the more faster hydrolysis of ester under acidic environment and further played an important role in excellent antitumor activity [93]. Liu et al. developed a simple one-step esterification reaction between C-2′-OH of PTX and a carboxyl functionalized cyclic to synthesize acid biodegradable tunable mPEG-polyPTX diblock copolymer nanoparticles with high water solubility and low systemic toxicity. The nanoparticles were reasonably stable at the pH of blood, while a faster release rate of PTX from a hydrolysable ester linker was observed at pH 5.5(late endosomes) and next induced significant tumor regression [69]. A novel endosomal pH-activatable paclitaxel micellar prodrug based on hyaluronic acid-*b*-dendritic oligoglycerol displayed the active targeting and effective treatment of CD44-overexpressing human breast tumor (Fig. 3d–f). PTX was readily conjugated to N3-dOG-vinyl ether via an acetal bond through a click-type reaction between 2′-hydroxyl group of PTX and the periphery vinyl ether. The release of PTX was slow at pH 7.4 but greatly accelerated at endosomal pH. Compared to Taxol, HA-dOG-PTX-PM showed significant antitumor activity against MCF-7 cells [67]. PTX was also conjugated onto water-soluble poly (ethylene glycol)-*b*-poly (acrylic acid) (PEG-PAA) block copolymers via an acid-labile acetal bond to the PAA block. These acetal-linked PTX prodrug micellar nanoparticles showed accelerated drug release under endosomal pH conditions in a pristine state and achieved specific and efficient cancer chemotherapy [94].

The pH degradable polymer–drug conjugate is synthesized through acidic linkages to achieve a conjugated drug delivery system with high drug loading, better tumor targetability, sustained drug release without burst effect but minimal long-term side effects. The pH-dependent controlled drug release is the key variable which is much critical to their efficacy. We believe that optimization of the linker using alternative chemistries may further improve the efficacy of these nanoparticles, but further in vivo study needs to be carried out.

Acid-labile chemical bonds in the construction of nanocarriers

These well-defined nanocarriers have been usually prepared by diblock, triblock and multi-armed copolymers containing polymer blocks linked with acid-cleavable groups through a click reaction, and followed by physical interactions to generate the nanocarriers of drug entrapment. Several acid-sensitive linkages have been tested in recent years for the development of these pH-responsive drug delivery systems, such as acetal, ketal, hydrazone and β-thioether ester [95–98].

Acetal linkage allows facile design of pH-responsive nanocarriers for novel programmed drug release [99–102]. The linkage is relatively stable at neutral pH, but could be degraded under acidic conditions [103]. Hydrolysis of the acetals at mildly acidic pH is designed to reveal polar groups on the core-forming block, thus changing its solubility, disrupting the micelle and triggering drug release [104]. Chen et al. reported a novel pH-sensitive degradable polymersomes for triggered release of anticancer drugs. However, the acetals of polymersomes were stable at pH 7.4, prone to fast hydrolysis at acidic pH of 4.0, with half lives of 0.5 d. The acetal hydrolysis resulted in significantly enhanced drug therapeutic efficacy and minimal side effects [105]. The pH-sensitive degradation of acetals in asymmetric poly(ethylene glycol)-*b*-poly(trimethoxy benzylidene tris(hydroxymethyl)ethane methacrylate)-*b*-poly(acrylic acid) triblock copolymers triggered doxorubicin hydrochloride release in the endo/lysosomal compartments of cancer cells, resulting in high therapeutic effects [65]. Well-defined three-armed star-block copolymers containing poly(ethylene glycol) monomethyl ether (mPEG) and poly(ε-caprolactone) (PCL) blocks linked with acid-cleavable acetal groups could self-assemble into spherical micelles for pH-triggered and efficient intracellular drug delivery [106]. Mesoporous silica nanoparticles coated by poly(*N*-succinimidyl acrylate) or dextran on the surface via an acid-labile acetal linker showed lower premature drug release at neutral pH and efficient intracellular pH-responsive controlled release [107, 108].

Poly (β-thioether ester)s have aroused much attention as a class of acid degradable functional groups that can provide opportunities for pH-selective targeting in their unique manners [109, 110]. Unlike other acid liable moieties, such as hydrazone, acetal and ketal, the β-thiopropionate groups in their polymer backbone can be cleaved selectively under mild acidic conditions (pH ~ 5.5) at a very slow rate by contrast [110–112]. And the β-thiopropionate is more sensitive to acid than the ordinary ester bond because the lone pair electrons of the sulfide atom at the β-position of the carbonyl may facilitate the formation of a four-membered ring, which can be attacked by water molecules [113]. In addition, this linker can be generated with ease by a facile thiol–acrylate Michael reaction [114]. Oishi et al. employed a strategy to formulate pH-sensitive and targetable micelles of siRNA based on the novel Michael addition of 5-thiol-modified siRNA toward lactosylated PEG through acid-labile linkage of β-thiopropionate, followed by the complexation with poly (L-lysine). The β-thiopropionate was readily cleaved at the pH corresponding to that of the intracellular endosomal compartment (pH 5.5), which revealed a targetable siRNA delivery system used in a practical context [115]. Chen et al. prepared well-defined chitosan nanocapsules by the UV-induced thiol–ene miniemulsion cross-linking of N-maleoyl-functionalized chitosan. With acid-labile β-thiopropionate cross-linkages, the DOX-loaded chitosan-based nanocap-

Table 2 List of biotherapeutic molecules delivered by pH-sensitive nanocarriers

Biotherapeutic molecules incorporated	Polymeric nanocarriers	Significant effects	References
Iodinated boron dipyrromethene photosensitizer	Mannose prodrug nanoparticles (Schiff base)	Enhanced near infrared imaging-guided photodynamic therapy	[12]
Bovine lactoferricin	HA-poly(acrylamide-co-acrylonitrile)-PEG nanoparticles	Cationic anticancer peptides delivery and improving antitumor immune responses	[122]
siRNA	Mn(iii)- and Mn(iv)-integrated nanocomposites	Rapid T1-weighted imaging performance and enhanced therapeutic effects with the modulation of the TME	[123]
Dopamine	Functionalized mesoporous silicon nanoparticle with boronic-ester bond	Tumor blood vessel normalization and improved effect of DOX	[121]

sules exhibited enhanced acid-triggered release behavior at pH 5.5 [116]. Pramanik et al. have shown a simple strategy for the fabrication of pH-responsive polymeric drug-delivery scaffold for sustained release. The slow hydrolysis of the β-thiopropionate linkage gradually removed the hydrophobic moiety linked to the polymer backbone, eventually converted the amphiphilic polymer to a hydrophilic one and, consequently, the micellar aggregation was disassembled leading sustained release of the entrapped DOX selectively at pH 5.2, making this scaffold an attractive platform for targeted cancer therapy [117]. Very recently, it is of great interest to insert acid-labile β-thiopropionate linkages in the main chain of the hydrophobic block to design multi-stimuli responsive micelle with a more versatile and complex level of control [118]. Yang and coworkers have successfully demonstrated that β-thiopropionate-poly (ethylene glycol)-modified Fe_3O_4@$mSiO_2$ nanocomposites could be used for pH-controlled drug release. Fe_3O_4@$mSiO_2$ core–shell nanoparticles are used as the host, and pH-sensitive β-thiopropionate-poly (ethylene glycol) was employed to graft outside of Fe3O4@mSiO2 as the blocking caps to inhibit premature drug release. Owing to the hydrolysis of the ester bond in an acidic environment (pH 5.8), DOX-Fe_3O_4@$mSiO_2$@P2 was regarded as pH-sensitive release and promising applications for multifunctional nanocarriers in smart sites and time- and dose-selected drug release [119]. Jin et al. have prepared a novel amphiphilic ABA-type triblock copolymer poly (ethylene glycol)-*b*-poly (ethanedithiol-alt-nitrobenzyl)-*b*-poly (ethylene glycol) with light- cleavable *o*-nitrobenzyl linkages and acid-labile β-thiopropionate linkages repeatedly in the main chain of the hydrophobic block by sequential thiol–acrylate Michael addition polymerization. The anticancer drug doxorubicin could release from the micelles self-assembled by the triblock copolymer in light-induced rapid burst release and pH-induced slow sustained release owing to the different degradation chemistry of *o*-nitrobenzyl linkages and β-thiopropionate linkages [120]. These multi-responsive polymers have a great potential for sustained intracellular drug release in targeted drug delivery.

Special delivery platforms in biomedical technologies

The pH-sensitive smart polymeric nanocarriers nanotechnology revolution has led to another array of delivery platforms in biomedical technologies covering photosensitizer, gene, cationic anticancer peptides, etc. Some pH-sensitive polymers were described below according to the classification of biotherapeutic molecules incorporated (see Table 2). Mohammad et al. designed a pH-responsive mesoporous silicon nanoparticle (MSN) to targeting delivery a chemical messenger dopamine. The dopamine was loaded by reacting with phenylboronic acid conjugated with amine molecules of MSNs. In a weakly acidic pH of the tumor extracellular matrix, MSN smartly released dopamine due to the hydrolysis of boronic-ester bond between dopamine and functioned MSN, inducing tumor blood vessel normalization and providing an auxiliary treatment for cancer chemotherapeutic drugs [121].

The pharmacokinetics of pH-sensitive nanocarriers

Major limitations in the application of anticancer drugs include their no specificity, wide biodistribution, short half-life, low concentration in tumor tissue and systemic toxicity. The nanocarriers have effective potential to alter drug pharmacokinetics and biodistribution. This is particularly useful to avoid the rapid metabolism or clearance of the drugs.

As we know, high density of PEG on the surface of nanocarriers can prevent protein adsorption and evade the reticuloendothelial system (RES) and thereby prolong circulation and accumulate preferentially in tumor sites while, on the other hand, suppresses the cellular internalization [124]. However, there are still noticeable gaps that need to accomplish its perfect dialectical unification under both normal and tumor environment. PEG modification of acid cleavage linker as recently emerged as an attractive technique for overcoming PEG-dilemma [59, 125]. Ding et al.

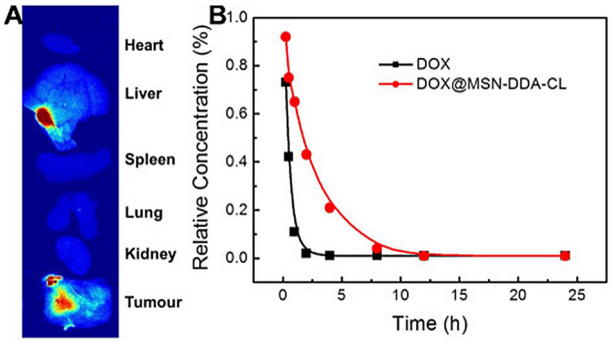


Fig. 4 In vivo tissue distribution of DOX@MSN-DDA-CL (**a**) and pharmacokinetics curves of DOX and DOX@MSN-DDA-CL in H22-bearing mouse animal mode (**b**) [128], Copyright 2016 Elsevier Ltd

described a PEGylated cell-penetrating peptide(CPP) modified pH-sensitive liposomes (CPPL) [126]. The liposome was constructed from a CPP attached phospholipid bilayer core and tethered PEG derivative by conjugating PEG with stearate via acid-degradable hydrazone bond. Pharmacokinetics results in normal rats showed similar long-circulating characteristics of CPPL as that of PEGylated liposomes, which proved that the CPP-modified pH-sensitive PEGylated liposomes could keep stable under physiology pH whereas have great potential to penetrate tumor cells under acidic condition. Moreover, ex vivo assay also confirmed that 4% CPPL could enhance the targeting efficiency of liposomes for breast tumors and reduced the accumulation in normal organs and tissues, especially in spleen.

pH-sensitive drug delivery system is useful to avoid the rapid metabolism or clearance of free drugs, and alters their pharmacokinetics and biodistribution to accumulate the site of pharmacological action [127]. Zhang et al. synthesized cross-linked prodrug to avoid elimination of premature drug release, and the improvement of pharmacokinetics during circulation and selective release of drug in cancer cells owing to the presence of hydrazone-bonded doxorubicin [66]. Chen et al. fabricated the novel pH-Sensitive drug delivery system based on modified dextrin coated mesoporous silica nanoparticles (DOX@MSN-DDA-CL) which release DOX more quickly compared with that at pH 7.4 due to the hydrolyzed of pH-sensitive Schiff's base at pH 6.0. Moreover, from Fig. 4a, the accumulation of DOX@MSN-DDA-CL in tumor was significantly higher than in heart, spleen, lung and kidney. Compared to pure DOX, DOX@MSN-DDA-CL kept a relative higher concentration in bloodstream from the pharmacokinetics curves (Fig. 4b) that $t_{1/2}$ of both samples were 0.41 h and 1.84 h, and the $AUC_{0\rightarrow 24\,h}$ of both samples were 0.66 h^{-1} and 2.57 h^{-1}, respectively [128].

Overall, these antitumor drugs can be encapsulated in the pH-sensitive drug delivery systems, represented a relatively safe and promising strategy to extend drug retention, lengthened the lifetime in the circulation at neutral pH, followed hydrolyze of the acid liable linkage and allowed controllable drug release in the desirable sites under acidic environments in tumor.

Conclusion

pH-responsive drug delivery systems with desired properties promote great potential in cancer therapy. The smart drug delivery systems reviewed are those with versatile chemical structures allowing them to bear stimuli-responsive groups to readily modulate drug release triggered by tumor acidic pH and improve drug pharmacokinetics. These pH-sensitive polymeric prodrugs were composed of antitumor drugs bounded to the polymer via acid liable linkers. These pH-sensitive copolymeric nanocarriers were prepared by diblock, triblock and multi-armed block copolymers containing polymer blocks linked with acid-cleavable groups through a click reaction, and followed by physical interactions to generate the nanocarriers of drug entrapment. Several acid-sensitive linkages were reviewed to construct these pH-responsive drug delivery systems, such as acetal, ketal, hydrazone, *cis*-aconityl linker and β-thioether ester. Nanocarriers were kept stable at neutral pH 7.4, while the sensitive linkage of those hydrolyzed at the tumor acidic microenvironment as pH dropped to around 5.0–6.0. These nanocarriers also could detach the PEG coated on the surface of nanocarriers and provided an opportunity to alter drug pharmacokinetics and biodistribution, facilitate drug accumulation in tumor cells and then uptake. Consequently, it controlled cargo drugs to release by degradation-mediated activation in the acidic conditions. Apart from the progress of the nanocarriers based on acid-liable bonds reviewed in this article, various pH-sensitive targeting strategies can be accomplished by charge reverse, pH-sensitive peptide, etc., which needs to be paid close attention to. Although considerable efforts have been reported, most pH-sensitive delivery systems are still in the early stages of preclinical technical validation and have not entered clinical translation. We believe that pH-sensitive polymeric nanocarriers with efficient delivery capacity will in the coming years serve as smart theragnostic agents for ongoing development of biomedical technology.

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Compliance with ethical standards

Conflict of interest The authors confirm that this article content has no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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