The Development and Achievement of Polymeric Nanoparticles for Cancer Drug Treatment

Wing-Hin Lee, Ching-Yee Loo, Paul M. Young, Daniela Traini and Ramin Rohanizadeh

Abstract

Limited aqueous solubility, stability, and bioavailability are common characteristics of hydrophobic drugs which impedes the delivery of drugs to intended site of action. In recent years, polymeric nanoparticles as drug delivery vehicle are widely used in various chronic disease therapies owing to their favorable features such as versatility, biocompatibility, biodegradability, and biomimetic characters. In the field of smart drug delivery, polymeric nanoparticles have improved specificity toward targeted site of action, reduced toxicity, and prolonged residency time in vivo. To date, various successful marketed clinical use products of polymeric nanoparticles include Genexol-PM and Abraxane® (cancer), Capaxone® (multiple sclerosis), Peglntron® (hepatitis C), Cimzia™ (rheumatoid arthritis), and Micera® (kidney failure). Ideal requirements of polymeric nanoparticle systems often include effectively controlled particle size, alterable surface chemistries, enhanced solubility, and therapeutic index of active drugs at predetermined rate and time. For instance, conjugation of polymeric nanoparticles with ligands is beneficial to avoid macrophage clearance and achieve long-circulation in vivo. This chapter will provide an overview of the achievement of polymeric nanoparticles which exhibit passive and active

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targeting, stimuli-triggered releases of chemotherapeutic drugs and therapeutic implications both in vitro and in vivo. In addition, the scope of successful translation polymeric nanoparticle system into clinical practice and future considerations will be outlined in the review.

Keywords
Polymeric micelles · Cancer · Nanoparticles · Nanomedicines

1 Introduction

Cancer is the leading cause of death in developed countries and is projected to surpass cardiovascular disease in terms of number of cases in near future. Statistics revealed that in 2008 more than 12 million new cancer patients were diagnosed and a staggering 8 million of deaths in the same year (Bray et al. 2013). From the socioeconomic point of view, due to escalated unhealthy lifestyles and aging population, cancer disease has contributed to significant economic burden to countries. For example, the National Institutes of Health in United States has provided $227 billion to cost of cancer treatment in 2007 (Popat et al. 2013). Cancer is characterized as group of cells which does not adhere to normal cell growth cycle processes. These phenomena was contributed by external factors that mainly related to the lifestyle such as smoking, unhealthy diet, and lacking of physical activities; however, internal factors are highly affected by the variation of genetic or epigenetic which related to genetic mutations and interruption of expressing inflammations markers (Doll and Peto 1981; Willet 2001; Calle et al. 2003; Hanahan and Weinberg 2000, 2011). Current standard protocols for cancer treatment include size reduction of tumor, surgery, radiotherapy, and chemotherapy. For nonmetastatic, primary cancers, surgery, and radiotherapy are most appropriate and effective treatment method (Brannon-Peppas and Blanchette 2012). However, these methods lack responsiveness from patients harboring multidrug-resistant, metastatic cells. At metastatic stage, chemotherapy is the preferred method in order to ensure the circulation of chemotherapeutic drugs to reach other parts of body via bloodstream. It is undoubtedly that chemotherapeutic drugs are effective to inhibit rapid proliferation of cancer cells (Brannon-Peppas and Blanchette 2012). However, the inherent toxicity inflicted by these drugs impacted the survival of healthy cells simultaneously during treatment course. More specifically, some of these compounds are not compatible in maintaining bone marrow and intestinal epithelium. This has significantly contributed to the failure to improve patients' survival. The ballooning cancer incidence has increased the pressure to develop effective methods to deliver chemotherapeutic drugs to the patient. However, it is important to understand the limitation factors of drug delivery that contributed to the failure in treating cancer disease (Iyer et al. 2013). Despite the advances in cancer research, our understanding

in cancer treatment is still limited. Current urgent need for cancer treatment is the discovery of novel biocompatible and side-effect free therapeutics with singular ability to eliminate cancer or solid tumor while leaving the healthy cells untouched. To further understand or design better cancer treatment method, we should understand the role of physiological barriers in tumor/cancerous cell and the effect of physicochemical properties of the chemotherapeutic drugs in cancer treatment. These two factors were identified as the main barrier in cancer treatment by lowering the cellular concentration of chemotherapeutic drugs.

1.1 Physiological Conditions of Tumor Tissues

Tumor tissues exist in abnormal microenvironments such as vascular abnormalities, oxygenation, perfusion, pH, and metabolic states (Vaupel et al. 1989). During initial growth of solid tumor (<1–2 mm^3), both supplies of nutrients and oxygen are readily accessible to tumor cells via diffusion and they are dependent on blood supply (Vaupel et al. 1989). However, once the tumor sizes have exceeded 2 mm^3, the supply of oxygen and nutrients becomes limited and the cells fall into realm of hypoxia. As a result, tumor cells respond by recruiting new blood vessels (known as angiogenesis) via activating the transcription of cellular hypoxia-inducible factor, thereby activating expression of cascade inducible growth factors such as the vascular-endothelial growth factor (VEGF), the platelet-derived growth factor (PDGF), and the tumor necrosis factor-α (TNF-α) (Folkman 1995; Bates et al. 2002). During the formation of new blood vessels, these immature vasculatures are subjected to various remodeling process, however, this processes are normally not complete and result in dilated, tortuous, and heterogeneous blood vessels (Jain and Stylianopoulos 2010). In addition, they are disorderly branched, have irregular capillary bed and pore size from 200 to 2000 nm (Hobbs et al. 1998). Owing to the heterogeneous blood vessels, the flows of blood through tumor vessels are highly depended on the type of tumors and their microenvironment conditions (Jain 1989; Hobbs et al. 1998). This has directly resulted in poor drug penetration into tumor. In addition, poorly organized structure of solid tumors is also another factor which limits the delivery of drugs into the larger tumors.

In addition, due to the abnormal structure of lymphatic vessel in solid tumor, the level of tumor interstitial fluid pressure (IFP) are relatively higher compared to normal tissue which is approximately 0 mm/Hg (Swartz and Fleury 2007). The increment of IFP has served as a barrier for delivery of chemotherapeutic drugs into solid tumor and the situation is worsened especially dealing with high molecular weight drugs. The increase of IFP results in the reduction of transcapillary transport into tumor, thus contributing extremely low concentration of drugs in tumor region (Jain 1989). In addition, IFP is relatively higher in the central of tumor and this IFP activity is likely to create a mass flow movement of fluid out from the central of tumor. Thus this once again diminishes the optimal concentration of drugs inside the central of tumor (Padera et al. 2004).

For healthy cells, the extracellular pH (pH_e) and intracellular pH (pH_i) are stringently maintained at pH 7.4 and 7.2, respectively (Wike-Hooley et al. 1984).

However, the pH is reversed ($pH_i > pH_e$) in most tumor tissues. It should be noted the variation of pH_e depends on the tumor histology, volume and location of the tumor. The low extracellular pH is primarily owing to rapid growing and angiogenesis of cancer cells which cause rapid depletion of oxygen and shift toward anaerobic glycolysis leading toward buildup of lactic acid in the tumor interstitium (Mura et al. 2013; Wike-Hooley et al. 1984; Biswas et al. 2016).

1.2 Rationale of Cancer Nanotechnology

Cancer nanotechnology is believed to provide cutting-edge advances in cancer detection, diagnosis, imaging, and treatment, which involve the integration of various disciplines including biology, chemistry, engineering, and medicine. Nanotechnology is typically defined as materials with sizes in the 1–1000 nm for at least one dimension and synthesized using both top-down and bottom-up methods (Mura et al. 2013). It is established that nanoparticles exhibit unique properties based on the size, shape, or functionality that are not seen when existing as bulk sold solids. Recent trends have emerged on the use of superparamagnetic iron oxide nanoparticles as both contrast and hyperthermia agents for cancer detection (Schleich et al. 2013; Schweiger et al. 2011; Zhao et al. 2015a, b; Wu et al. 2015; Thomas et al. 2015; Quinto et al. 2015). Meanwhile, other semiconductor and metal nanoparticles are under intense scrutiny as potential diagnostic biomarkers and molecular profiling studies (Devi et al. 2015; Vidotti et al. 2011). Effective early detection of neoplastic lesions is crucial to improve the survival of cancer patients and yet remains a far-fetched goal. Current clinical imaging techniques lack the sufficient resolution for early detection (Devi et al. 2015; Vidotti et al. 2011). The use of multifunctional nanoparticles comprising of contrast agents covalently linked to targeting agents or recognition molecules such as antibodies in conjunction with existing imaging technologies may significantly improve the chances of early cancer detection (Taleat et al. 2014). In addition, nanoparticles also offer the possibility of simultaneous tumor imaging and treatment, as various functional groups could be chemical conjugated on the surface of nanoparticles (Han et al. 2016; Bwatanglang et al. 2016; Ma et al. 2015; Li et al. 2015a, b, c, d, e). Another significant impact of nanotechnology is optimized drug delivery in which nanocarriers are adaptable to encapsulate various drugs including hydrophobic/hydrophilic molecules, peptides, antibodies, and nucleic acids (Tangsangasaksri et al. 2016; Jones et al. 2016; Corbet et al. 2016; Zhao et al. 2015; Yin et al. 2015). In addition, functional nanoparticles could be covalently decorated with specific biological molecules to enhance the targeting and uptake by specific tissue (Gao et al. 2015a, b; Liu et al. 2015a, b; Baek et al. 2014). Meanwhile, surface coating of nanoparticles with stealth-like polymer results in increased blood circulation and retention of drugs (Leal et al. 2015; Kooijmans et al. 2016). Additionally, therapeutic molecules existing within the nanoparticles are usually protected from degradation, hence, the significantly higher stability of drugs in vivo. Nanoparticles could be engineered to either release drugs in a sustained release manner or stimuli-triggered release manner (Scheeren et al. 2016; Gao et al. 2015a, b).

1.3 Important Considerations in Nanoparticle-Based Delivery for Cancer Treatment

In the context of nanoparticle-based drug delivery for cancer therapeutics, several important aspects have to be considered. They are passive and active targeting in which the former exploits the enhanced permeability and retention (EPR) effect while the latter is focused on targeting specific overexpressed receptors and surface molecules in tumors (Fig. 1). Other factors include physicochemical characteristics of nanoparticles (particle size, charge, and shape) and subtle microenvironments variations between healthy and cancer cells (pH, redox potential, temperature, and enzyme expression) (Bertrand et al. 2014).

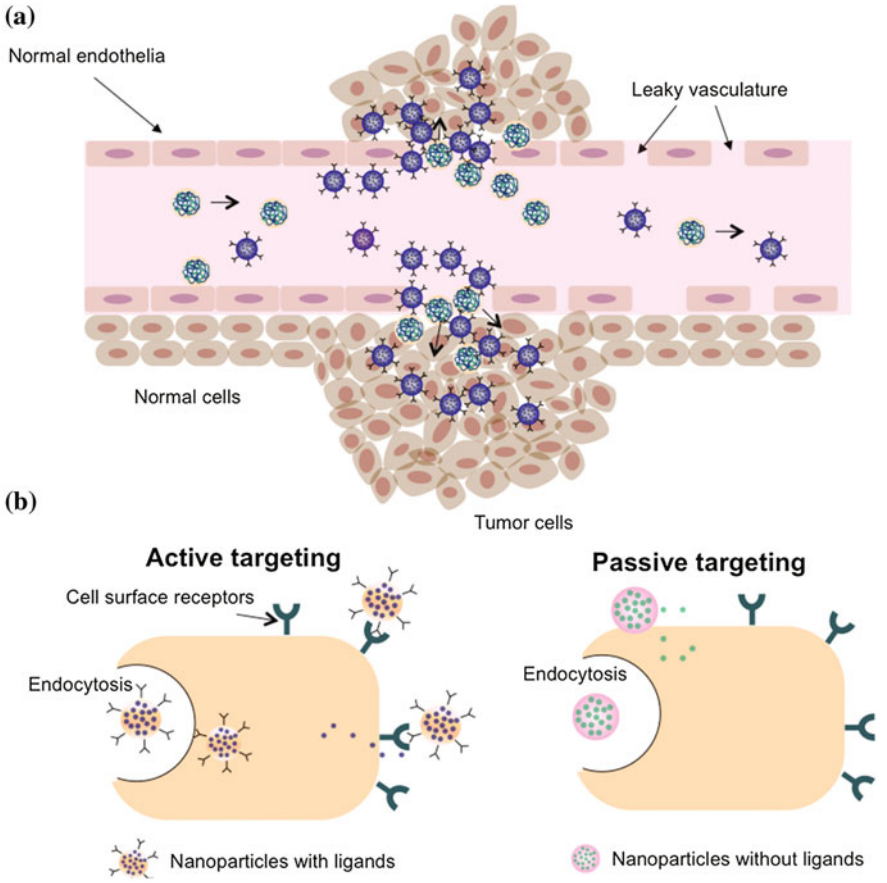


Fig. 1 **a** Schematic representative showing the exploitation of enhanced permeability and retention (EPR) effect by nanoparticles (with or without targeting ligands) to exit blood vessels through leaky vasculature, accumulate within tumor tissues, and subsequently internalized into cells via endocytosis. **b** Differences in the internalization mechanisms of nanoparticle through passive and active targeting. Adapted and modified from Lee et al. (2014)

1.3.1 Passive Targeting of Nanoparticles: Enhanced Permeability and Retention (EPR) Effect

Most nanoparticle-based delivery systems available in the market employ passive targeting approach by exploiting unique tumor microenvironments, which include leaky tumor microvessels and malfunctioned lymphatic drainage systems. The former results in enhanced permeability toward macromolecules relative to healthy tissues whereas the latter causes higher fluid retention in tumor interstitial space (Bertrand et al. 2014). These characteristics, otherwise known as enhanced permeation and retention (EPR) effect has been capitalized to foster at least 100× higher accumulation of nanoparticles in perivascular tumors' microenvironment compared to soluble drugs. The fundamental principles and factors contributing to EPR effect were comprehensively reviewed recently (Bertrand et al. 2014).

Tumor vasculatures are often disorderly branched, and are dilated with large interendothelial junctions and leaky vessels (Hobbs et al. 1998). These result in large capillary pore size ranging from 100–2000 nm in diameter (Hobbs et al. 1998). In contrast, the pore size for normal vessels is 5–10 nm in diameter. These unusually large pores allow higher permeability in tumor thus enabling nanoparticles to pass into tumor. This phenomenon forms the enhanced permeation of the EPR effect. Secondly, solid tumors are generally characterized with impaired lymphatic systems as rapidly proliferating cancer cells compress lymphatic cells causing the collapse of most vessels. These compromised lymphatic vessels lead to poor drainage of interstitial fluid in tumor. This forms the enhanced retention aspect of the EPR effect.

Physicochemical characteristics of nanoparticles such as size, shape, and surface charges have been instrumental to influence the extent of nanoparticles extravasation. As a rule of thumb, the particle sizes should be smaller than the cut-off diameters of the fenestrations in the neovasculature, which ranges between 100 and 2000 nm depending of type of tumor. Cabral and coworkers compared the accumulation of sub-100 nm polymeric micelles particles on both hyperpermeable and poorly permeable tumors (Cabral et al. 2011). These micelles were found to localize and accumulate evenly in hyperpermeable tumor (murine colon adenocarcinoma) irrespective of particle sizes (30, 50, 70, and 100 nm). However, in poorly permeable tumor (human pancreatic adenocarcinoma), only particles with diameters smaller than 70 nm could be internalized in the tumor (Cabral et al. 2011). Besides size, surface charges of a nanoparticle could modify recognition, opsonization, internalization, and plasma circulation kinetic (Alexis et al. 2008; Levchenko et al. 2002; Xiao et al. 2011).

Positively charged liposomes were also found to possess stronger affinities toward negatively charged phospholipid groups found in tumor endothelial cells. Results from animal model suggested that positively charged nanoparticles with sizes ranging from 50 to 100 nm enhanced penetration and accumulation of drugs in tumor (Davis et al. 2008). Steric stabilization with PEGylation on the surface of nanoparticles imparts stealth properties by helping them to evade opsonization and clearance by RES; thus making these nanoparticles long circulating (Lin et al. 2012). Nevertheless, it has been suggested that EPR effect is much more complex

than initially thought as other biological process such as angiogenesis, vascular permeability, hemodynamic regulation, heterogeneities in tumor genetic profile, and tumor microenvironments are involved in tumor growth and vary according to cancer patients. Therefore, the designing of nanocarriers have to take into consideration these biological processes rather than just focusing on EPR alone.

1.3.2 Active Targeting of Nanoparticles

Active targeting also known as ligand-mediated targeting is achieved by peripheral conjugation of targeting moieties to surface of nanoparticles for specific delivery systems. In most cases, ligands decorated nanoparticles are chosen for specific recognition to overexpressed receptors and surface molecules in tumors. The first active targeted delivery was described in late 1970s based on the concept of coating antibodies to nanoparticles' surface to allow interactions with target antigens. To date, representative ligands include peptide, transferrin, aptamers, growth factor, folate, antibodies, or antibody fragments (Liu et al. 2016; Zhou et al. 2013; Singh et al. 2016; Guo et al. 2011; Shargh et al. 2016; Yamamoto et al. 2014). Two common approaches are used in ligands-mediated targeting: (i) to target tumor cell surface receptors and (ii) to target tumor microenvironments. Targeting the cell surface receptors present in tumors is beneficial to increase cell–drug association while eliminating nonspecific interactions with healthy tissues. Meanwhile, tumor microenvironment such as the extracellular matrix and intracellular signaling genes is often targeted to activate immune response and angiogenesis. For effective active targeting, ligand moieties should be in close proximity with target receptors. Again, systemic clearance of ligands-mediated nanoparticles also affects the bioavailability of therapeutics in bloodstream to tumor. As the blood flow in tumor is low, the loss of nanoparticles via clearance sometimes overwhelms the increased affinities of nanoparticles toward tumors.

2 Polymeric Nanocarriers for Therapeutic Applications in Cancer

Polymeric micelles are self-assembled amphiphilic block or graft copolymer chains in aqueous conditions. Polymeric micelles are typically nano-sized, spherical, and exist as supramolecular colloidal particles with hydrophobic core and hydrophilic corona (Attia et al. 2011). The hydrophobic core serves to encapsulate and solubilize anti-cancer drugs while the hydrophilic compartment provides particles' stability against aggregation in aqueous microenvironment. Polymeric micelles are versatile and could accommodate different classes of hydrophobic molecules such as therapeutics, imaging and contrast agents for wide ranges of application. The most commonly used hydrophilic polymers for the preparation of micelles is poly (ethylene glycol), PEG (Li et al. 2014a, b, c; Liu et al. 2015a, b; Ruiz-Hernandez et al. 2014). To date other hydrophilic polymers include chitosan, poly(*N*-vinyl pyrrolidone) (PVP), and poly(*N*-isopropylacrylamide) (pNIPAAm) (Bailly et al.

2012; Movagharnezhad and Moghadam 2016; Abbasi et al. 2016; Yang et al. 2016). Meanwhile the polymers used to form the core of micelles include poly (lactide-*co*-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(β-aminoesters)P(bAE), distearoyl (phosphatidylethanolamine) (DSPE), and polyamino acids (Lee et al. 2015; Diao et al. 2010; Jin et al. 2007; Zhang et al. 2016a, b; Alavizadeh et al. 2016).

2.1 Polymeric Micelles for Therapeutic Applications in Cancer

2.1.1 Doxorubicin (DOX) Conjugated Polymeric Micelles

It is accepted that the encapsulation efficiency of drugs is dependent on the hydrophobic core of micelles; which in turn determines anti-cancer therapeutic efficacy (Table 1). In a recent study by Sun and coworkers, the extent of hydrophobicity of amphiphilicdi block copolymer containing PEG and polyphosphoester (PPE) on anti-cancer efficacy was investigated (Sun et al. 2014a, b). PPEs with different alkyl side chain length (butyl, hexyl, and octyl) were synthesized to fine-tune the hydrophobicity of micellar core (Sun et al. 2014a, b). The length of alkyl groups influenced release rate of doxorubicin and in vitro anti-cancer activity. Micelles with the least hydrophobicity demonstrated the highest killing effect of breast cancer cell line (MDA-MB-231), which might be attributable to the higher release rate of drug in vitro. Owing to prolonged circulation time and enhanced doxorubicin retention in tumors, PEG-PPOE (most hydrophobic core) micelles were considered as one the most effective micelles material to reduce tumor burden in vivo (Sun et al. 2014a, b).

Lee and coworkers developed a self-assembled, biocompatible triblock PEG-poly(amino acid)-based micellar system where doxorubicin was loaded via dialysis method. The poly(ethylene glycol)-poly(L-asparticacid)-poly(L-phenylalanine) [PEG-PAsp-PPhe] micelles could selectively release entrapped DOX at low intracellular pH, in endosomal compartments of MCF-7 (breast adenocarcinoma) cells (Lee et al. 2011). In a recent work, DOX was conjugated to methyl poly (ethylene glycol)-distearoylphosphatidylethanolamine (MPEG-DSPE) via thin film hydration method to produce near spherical micelles with particles size of 20 nm, which was the ideal size range lymph node metastasis targeting (Li et al. 2015a, b, c, d, e). These micelles efficiently evaded macrophage clearance and demonstrated higher uptake by A375 cells in vitro in comparison to MPEG-DSPE/Rhodamine B micelles. Additionally, subcutaneous injection of MPEG-DSPE/DOX micelles to lymphatic metastatic mice model bearing A375 cells resulted in decrease of popliteal and iliac lymph nodes, an indication that the drug-loaded micelles were accumulated in the lymphatic drainage system (Li et al. 2015a, b, c, d, e). A multifunctional micellar system consisting of pH-responsive and bone targeting behavior was conceived to increase the efficacy of DOX in bone metastasis treatment (Ye et al. 2015). DOX was conjugated to PEG-alendronate (ALN) via acid cleavage hydrazine linkages and spontaneously self-assembled to form micelles

Table 1 Examples of ligands targeted polymeric micelles for active targeting of chemotherapeutic drugs

Polymeric materials	Drug	Active ligand	Targeting receptor	Remarks	Reference
Poly(ethylene glycol)–poly(aspartate hydrazoneadriamycin) [PEG–P (Asp-Hyd-ADR)]	Adriamycin (ADR)	Folate	Folate receptor	Significant cytotoxicity effect toward KB cells with folate decorated ADR-loaded micelles. This was contributed by the higher cellular uptake of ADR via receptor and ligand interaction	Bae et al. (2005)
Oligoethylene glycol methylethermethacylate and methyl acrylic acid	Cisplatin and oxoplatin	Folate	Folate receptor	Folate conjugated micelles encapsulating with drugs were only effective against folate-overexpressed OVCARS cells. In non-folate expressing cells such as A549, no significant enhancement was demonstrated	Scarano et al. (2013)
Poly(ethylene glycol)-*b*-poly(acryloyl carbonate)-*b*-poly(D,L-lactide) [PEG-PAC-PLA]	PTX	Folate	Folate receptor	PTX-loaded micelles (either cross-linked or non-cross-linked) were highly toxic toward KB cells. The toxicity effect of folate decorated PTX-loaded micelles was contributed by higher cellular uptake via folate receptor-mediated endocytosis	Xiong et al. (2011)
PHIS–PEG and Fol–PEG–PLA	DOX	Folate	Not mentioned	Folate decorated DOX-loaded micelles with pH-sensitive characteristics were superior to suppression MCF-7ADR proliferation. In vivo, this micellar formulation was not only effective to reduce tumor volume; it was also nontoxic to mice. The survival of mice receiving DOX-loaded micelles was 100% compared to only 60% receiving free DOX	Li et al. (2015a, b, c, d, e)
Polyethylene glycol-dextran (PEG-HMD)	PTX	Folate	Not mentioned	PAX loaded folate decorated PEG-HMD micelles significantly decreased the IC_{50} values of HeLa and M109-HiFR cells line compared to Taxol. The prepared dry powder formulation	Rosiere et al. (2016)

(continued)

Table 1 (continued)

Polymeric materials	Drug	Active ligand	Targeting receptor	Remarks	Reference
				(void micelles, without PAX) was contributed nonstatistically differences in pro-inflammatory cytokine expression (IL-1β, IL-6 and TNF-α from mice lung tissue	
Poly(ethylene oxide)-*b*-poly(e-caprolactone) [PEO-*b*-PCL] or Poly(ethylene oxide)-*b*-poly(a-benzyl carboxylate-ε-caprolactone) [PEO-*b*-PBCL]	PTX	c(RGDfK) or p160 peptides	Not mentioned	Both p160 and c(RGDfK) modified polymeric micelles were highly selective toward MDA-MB-435 and HUVEC cell lines. p160 functionalized PTX-loaded micelles demonstrated more selective targeting toward tumor cells	Shahin et al. (2011)
Poly(lactic acid-*co*-glycotic acid) and poly (ethylene glycol)	PTX	H7K(R2)2 peptide	Not mentioned	The peptide conjugated PTX micelles were densely accumulated in tumor sites compared to non-peptide conjugated PTX micelles. At the same time, peptide modified formulation possessed the highest antitumor activity against MCF-7 tumor-bearing mice	Zhao et al. (2012)
Poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) [PEOz-PLA]	PTX	Cyclic RGDyK peptide	$\alpha_v\beta_3$	Cyclic RGDyK conjugated PTX micelles: (i) increased cellular uptakes in PC-3 cells via $\alpha_v\beta_3$ interaction on cell surface, (ii) rapidly release PTX in pH microenvironment mimicking endosomal-lysosomal compartments (iii) conferred negligible systemic toxicity and (iv) were remarkably effective in the suppression of tumor growth PC-3 xenograft bearing mice	Gao et al. (2015a, b)
Poly(ethylene glycol)-poly(D,L-lactic acid) PEG-PLA	DOX	AP (CRKRLDRN) peptides	IL-4 receptor	The confocal images revealed that the presence of AP peptides promoted higher cellular uptake. More than 4-fold decrease in tumor volume and weight in MDA-MB-231 tumor-bearing mice compared was noted 15 days of posttreatment	Wu et al. (2010)

(continued)

Table 1 (continued)

Polymeric materials	Drug	Active ligand	Targeting receptor	Remarks	Reference
Poly(ethylene glycol)-phosphatidylethanolamine (mPEG-PE)	R547	Transferrin	Transferrin receptor	R547 loaded transferrin targeted micelles showed higher toxicity compared to free R547 and nontargeted R547 micelles	Sawant et al. (2014)
Poly(lactic acid-*co*-glycolic acid) and poly (ethylene glycol) PLGA-PLA	Doxorubicin (DOX)	Monoclonal antibody; Hab18 $F(ab')_2$	Antigen	The toxicity of targeted micelles was proven to be effective in tumor cells (in vitro and in vivo). The survival fraction of HepG2 and Huh7 were reduced to approximately 0.2 after 24 h of treatment. In nude mice bearing HepG2 xenograft, the bioavailability of DOX was mostly found in tumor tissue when targeted micelles were used to deliver DOX. Thus, this contributed to higher efficiency in controlling the tumor growth in the mice model	Jin et al. (2010)
Poly(lactic acid-*co*-glycolic acid) and poly (ethylene glycol) PLGA-PLA	Gefitinib (GNB)	Mannose	Lectin	Mannose decorated GND loaded micelles resulted in higher cellular internalization, and subsequently caused higher apoptotic and necrotic activities in A549 cells. In addition, the stability of GNB in micelles was also improved for about 5-fold. GNB accumulations in in vivo tumor were increased 7-fold compared to free GNB	Wang et al. (2015a, b, c)
Methoxypoly(ethylene glycol)-grafted-poly (β-amino ester)	DOX	Biotin	Not mentioned	Biotin conjugated micelles improved the cellular uptake and effectively regulated the release of DOX in acidic conditions	Kim et al. (2012)

with particle size and loading of 114 nm and 24.3%, respectively (Ye et al. 2015). Intravenous administration of PEG-ALN/DOX micelles to tumor-bearing mice exhibited higher drug retention in bone metastatic tumor tissue, delayed tumor growth, decreased bone loss, and reduced cardiac toxicity in vivo (Ye et al. 2015). Kim and coworkers have successfully synthesized DOX-loaded poly (ethylene oxide)-poly [(R)-3-hydroxybutyrate]-poly (ethylene oxide) (PEO-PHB-PEO) triblock polymeric micelles with excellent drug penetration and distribution in an in vitro 3D spheroids tumor culture model (Kim et al. 2010). The PEO-PHB-PEO/DOX micelles were rapidly diffused into the core of spheroids within 30 min while free DOX was mostly sequestrated in acidic endosomes of cells close to vasculature. The enhanced penetration characteristic of micelles was seemingly due to the ability of PHB to form channels in cell membrane. Furthermore, PEO-PHB-PEO/DOX micelles induced apoptosis and inhibited tumor growth without significant systemic toxicity in tumor-bearing mice (Kim et al. 2010).

To improve the loading of DOX to PEG-PCL micelles, three different molecules with π-conjugated moieties (cinnamic acid, 7-carboxymethoxy coumarin, and chrysin) were functionalized to the terminal hydroxyl groups of PCL blocks (Liang et al. 2015). More than twofold increase in DOX loading was noted after the modification. Among the three modified PEG-PCL micelles, the presence of chrysin exhibited the most potent anti-cancer activity both in vitro and in vivo (Liang et al. 2015). In another study, chemical conjugation of DOX to succinic anhydride activated pluronic F68 was synthesized via linkage of primary amine group of DOX to carboxyl group of pluronic F68 (Zhao et al. 2011). Similar to other published literature, DOX-pluronic F68 micelles demonstrated higher cytotoxicity effect against A549 cells and could successfully circumvent the MDR of A549/DOX cells (Zhao et al. 2011).

Folate (FA)-receptor delivery of DOX-loaded poly(*N*-isopropylacrylamide-*co*-*N*, *N*-dimethylacrylamide-*co*-2-aminoethyl methacrylate)-*b*-poly(10-undecenoic acid) (P(NIPAAm-*co*-DMAAm-*co*-AMA)-*b*-PUA) polymeric micelles was synthesized in which FA was conjugated to the hydrophilic block of AMA (Liu et al. 2007). These FA-DOX-loaded polymeric micelles demonstrated higher internalization, and cytotoxicity in cancer cells with overexpressed FA receptors. For instance, the IC_{50} of DOX-loaded micelles with FA against 4T1 and KB cells were significantly lower than that of DOX-loaded micelles without FA (3.8 vs. 7.6 μg/ml for 4T1 and 1.2 vs. 3.0 μg/ml for KB) (Liu et al. 2007).

A novel cell penetrating peptide (CPP) mediated polymeric micelles as nanocarrier for DOX was recently synthesized through the introduction of octa-arginine (PArg) into the reduction-cleavable copolymers (Cui et al. 2016). The synthesized polyamide amine-*g*-polyethylene glycol/polyarginine/DOX (PAA-PEG/PArg/DOX) micelles were monodisperse, spherical with sizes ranging from 20 to 80 nm in diameter and displayed enhanced EPR effect in tumor sites. The in vivo distribution data of DOX-loaded micelles delivered via intravenous injection to 4T1 bearing mice revealed stronger fluorescence signals and directional aggregation at tumor sites. Meanwhile, free DOX solution was systemically distributed throughout the whole body with weaker fluorescent signal (Cui et al. 2016).

The PAA-PEG/PArg/DOX micelles exhibited excellent tumor growth suppression in tumor-bearing Babl/c mice model compared to PEG-PAA/DOX micelles (Cui et al. 2016).

FA-decorated PEG5 k-EB2/DOX micelles for active targeting and tumor inhibition with particle sizes of 20 nm demonstrated sustained release kinetics of DOX profile over a period of 80 h. In addition, intracellular uptake of FA-decorated-DOX-loaded micelles was facilitated in breast cancer cells (4T1.2) and drug-resistant cells (NCI/ADR-RES) and simultaneously inhibited the function of P-gp efflux pump. (Lu et al. 2014). To overcome MDR in colorectal adenocarcinomas, co-delivery of DOX and small interfering RNA (siRNA) with active targeting was employed (Amjad et al. 2015). The authors reported that FA-functionalized cholic acid-polyethylenimine (CA-PEI) loaded with DOX/siRNA micelles were positively charged (+12 mV), moderately sized (150 nm), and showed high affinities toward DOX (Amjad et al. 2015). Both FA-functionalized CA-PEI/DOX micelles and FA-functionalized CA-PEI/DOX/siRNA micelles enhanced overall in vivo antitumor activity through inhibition of tumor growth and induction of cancer cell death (apoptosis and necrosis). However, no significant differences between the two micelles were observed, thus indicating that the siRNA did not act synergistically to improve anti-cancer activity (Amjad et al. 2015).

2.1.2 Paclitaxel (PTX) Conjugated Polymeric Micelles

PTX is one the most common and effective chemotherapeutic agents to treat a variety of cancers including ovarian, breast, non-small lung cancer, etc., (Rowinsky et al. 1989; Crawford et al. 2013; Razi et al. 2015; Bernabeu et al. 2016; Lam et al. 2014). The commercial PTX (under the tradename of Taxol®) is currently formulated in the mixture of Cremophor® EL and ethanol. One main disadvantage of Taxol® is that the vehicle agent Cremophor® EL induces significant side effects which include severe hypersensitivity, neurotoxicity, nephrotoxicity, and myelosuppression (Kumar et al. 2010). This section describes current designs of polymeric micelles systems proposed as nontoxic alternative vehicle to overcome the shortcomings of Cremophor® EL. Recently, a novel self-assembling diblock copolymer comprised of CL, trimethylene carbonate (TMC), and PEG_{750} has been found to form micelles spontaneously in water. The encapsulation of anti-cancer drugs such as PTX into the micellar core requires simplistic approach without needing organic solvent, dialysis, or evaporation step (Liu et al. 2007). Owing to the high hydrophobic nature of PCL/TMC block segments, significantly higher (threefold higher) solubilization of PTX into PEG-PCL-TMC micelles was achieved (Danhier et al. 2009a, b, c). Danhier and coworkers elaborated that PTX-loaded PEG-PCL-TMC micelles exhibited higher tolerance in mice compared to Taxol® irrespective of administration route. The maximum tolerated dose (MTD) of PTX-loaded PEG-PCL-TMC micelles delivered via intraperitoneal and intravenous route was 45 and 80 mg/kg, respectively. Meanwhile the MTD for Taxol® was 13.5 and 13.5 mg/kg, respectively (Danhier et al. 2009a, b, c). As expected due to higher dose tolerance, PTX-loaded PEG-PCL-TMC micelles were more effective to induce tumor growth retardation (Danhier et al. 2009a, b, c).

In another study, Zhang and coworkers proposed the use of PCL-PEG-PCL triblock copolymer as nano-vehicle for delivery of PTX via intravenous administration (Zhang et al. 2012a, b). PTX was incorporated into polymeric micelles via thin hydration methods and these resultant PTX-loaded micelles exhibited core-shell like morphology with average diameter of 93 nm, which fitted into the particle size window for passive targeting via EPR effect (Zhang et al. 2012a, b). The authors also compared the pharmacokinetic of PTX-loaded micelles with Taxol® after intravenous administration to rats (PTX dose: 7.5 mg/kg). PTX-loaded micelles had longer systemic circulation time and slower plasma elimination rate compared to Taxol® as evident from the area-under-curve (AUC) and mean residence time (MRT). Encapsulated PTX were 4.3-fold and 12.0-fold higher, respectively, than free PTX (Zhang et al. 2012a, b). Histopathological analyses, behavioral and body mass changes in EMT6 breast tumor-bearing rats revealed that PTX in the form of micelles enhanced therapeutic efficacy (reduced tumor size and evident coagulative necrosis) while simultaneously reduced its systemic toxicity (no significant behavioral changes and body mass reduction in rats) (Zhang et al. 2012a, b).

Linear-dendritic block copolymers using cholic acid (CA) as the building block have been reported to self-assemble into stable micelles in water. However, drug loading capacities of linear CA-PEG conjugates and star-shaped CA-PEG micelles were limited. Recently, telodendrimer PEG-CA, with a dendritic oligomer of CA conjugated on one end of linear PEG was designed which formed stable micelles in water with PTX loading efficiency of 36.5% (Xiao et al. 2009). In vivo efficacy of PEG-CA/PTX micelles were evaluated in both subcutaneous and intraperitoneal ovarian cancer mouse models and demonstrated superior antitumor activity with respect to Taxol® and Abraxane® (Xiao et al. 2009).

Another class of common amphiphilic block copolymers used as nano-micellar carrier is pluronic (PEO-PPO-PEO). In selected studies by the Fang's group, mixed or single pluronic polymeric micelles were chosen as carrier of PTX to achieve thermodynamically stable particles, increased drug loading rate, low immunogenicity relatively longer systemic circulation time, slower plasma elimination rate and higher PTX accumulation in tumor-bearing mice (Zhang et al. 2010a, 2011a, b). They have demonstrated the MRT of PTX-loaded pluronic F127/P123 micelles in the lung was 3-fold higher than commercial Taxol® (Zheng et al. 2010). More significantly, the tumor volume of A549 tumor-bearing rats 28 days after receiving PTX-loaded mixed micelles was only 31.8% that of Taxol® (Zheng et al. 2010). In addition, PTX-loaded pluronic F127/P123 micelles were also significantly effective against metastatic tumors (Zhang et al. 2011a, b).

Apart from synthetic polymers, natural polysaccharides such as hyaluronic acid (HA) and cell membrane like phospholipids (PE) are also considered as potential micellar carrier of PTX (Saadat et al. 2014a, b) (Table 1). In a recent study, two different PEs including dimiristoyl (phosphatidylethanolamine) (DMPE) and DSPE were investigated as hydrophobic block segments in combination with HA for encapsulation of PTX (Saadat et al. 2014a, b). HA-DMPE copolymers or HA-DSPE copolymers were linked via amide bonds using carbodiimide chemistry conjugation, and was subsequently sonicated in water to form mixed micelles (Saadat et al. 2014a,

b). The PTX loading and release rate for HA-DSPE micellar system 59.9% and 34 h, respectively, whereas, in comparison for HA-DMPE/PTX micelles, PTX was released at a higher rate (23 h) (Saadat et al. 2014a, b).

It is well established that transferrin receptor (TfRs) are overexpressed in human cancer and have been studied in detail in breast cancer, prostate cancer, myeloid leukemia, etc. (Table 1). In a recent work, surface transferrin-conjugated micelles were constructed to introduce the specific binding to TfR in cell membrane. The hybrid micelles were synthesized by mixing amphiphilicmal-PEG-*b*-PLA, with a maleimide group at the end of the PEG segment, and m(PEG-*b*-P(LA-*co*-MCC)/PTX followed with transferrin functionalization on outer surface of micelles (Yue et al. 2012). Coupled with PTX, these transferrin-modified micelles were accumulated at higher extent in nude mice bearing subcutaneous TfR-overexpressing cancer and also demonstrated stronger antitumor effect in SGC-7901 gastric carcinoma model (Yue et al. 2012).

2.1.3 Other Chemotherapeutic Drugs Conjugated Polymeric Micelles

Cabazitaxel (CBZ) is a second-generation taxane designed specifically to treat taxane-resistant tumors and has been approved by the US Food and Administration (FDA) for use in prostate cancer (Paller and Antonarakis 2011). Owing to a decreased propensity for P-gp mediated drug resistance, CBZ has been shown to be clinically effective in taxane-resistant metastatic breast cancer, advanced lung cancer, and metastatic prostate cancer (Mita et al. 2009). Like most taxane, CBZ is highly hydrophobic, water-insoluble; thus commercial CBZ under the tradename Jevtana® contains large amount of excipients (polysorbate 80 and ethanol) which leads to hypotension, bronchospasm, and erythema in patients (Mita et al. 2009). Zhuang and coworkers investigated the potential of CBZ-loaded mPEG-PCL micelles to overcome these disadvantages (Zhuang et al. 2016). Solid dispersion was used to encapsulate CBZ into monomethoxy polyethylene glycol-poly (ε-caprolactone) (mPEG-PCL) copolymers pre-synthesized via ring opening polymerization method. The mPEG-PCL/CBZ micelles had high drug loading (10.52%) with average size of 30 nm and sustained release kinetics in vitro. The apoptosis and cell cycle arrest was more pronounced for lung carcinoma cell line and LLC bearing mice when mPEG-PCL/CBZ micelles were used. This was in tandem with prolonged life span and tumor growth suppression in LLC bearing mice (Zhuang et al. 2016). Supramolecular pseudo-block copolymeric micelles with multiarmed star polymer as micellarexterior were recently investigated as potential CBZ carrier to treat drug-resistant A2780/T cell lines (Xie et al. 2015). Multiarmed β-cyclodextrin (βCD) grafted PVP was synthesized using combination of reversible addition–fragmentation chain transfer polymerization (RAFT) and click reaction and was non-covalently linked to linear PCL. PVP7-PCL micelles demonstrated high particle stability, low protein corona adsorption, and high CBZ encapsulation (Xie et al. 2015). The IC_{50} of free CBZ and CBZ-loaded PVP7–PCL micelles against A2780/T cells is 274 and 269 ng/ml, respectively. The authors noted that the cytotoxic effect CBZ-loaded PVP7–PCL micelles was much stronger compared

to free CBZ by taking into account that only approximately 65% of the loaded CBZ was released in 48 h (Xie et al. 2015).

Methotrexate (MTX) is amongst the first anti-metabolite drugs for cancer therapy and acts as a folate metabolite via competitive inhibition of dihydrofolatereductase to suppress conversion of folic acid to folate cofactors (Kaasgaard et al. 2009). MTX is commonly used in various cancer treatments such as childhood acute lymphocytic leukemia, osteosarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, head and neck cancer, lung cancer, and breast cancer (Seo et al. 2009). Pluronic F127-P105/MTX mixed micelles with pH-dependent characteristics was shown to have markedly increased blood circulation time of MTX and enhanced accumulation in tumor tissues of xenograft KBv bearing mice (Chen et al. 2013a, b). The IC_{50} values of Pluronic F127-P105/MTX mixed micelles and free MTX against KBv resistant cells were 0.073 μg/ml and >50 μg/ml, respectively. In addition, this micellar system induced much higher cell cycle arrest at phase G2/M compared to control (38.35% vs. 3.71%) (Chen et al. 2013a, b). The therapeutic activity of pluronic F127/P105-MTX micelles was further strengthened with the incorporation of a homing ligand receptor, FA on the outer surface of micelles (Chen et al. 2015). In addition to both caveolae- and clathrin-mediated endocytosis, FA-F127/P105-MTX micelles were also internalized via folate receptor-dependent pathways. Therefore, compared to nonspecific F127-P105/MTX micelles, the presence of homing receptor increased the accumulation in tumor regions by 1.5-fold. Nonspecific F127-P105/MTX micelles, however, were more localized in liver, spleen, and kidney (Chen et al. 2015). Other recent studies using variants of polymeric micelles as carrier of MTX also showed similar enhanced anti-cancer efficacy and higher drug's stability (Ren et al. 2015; Fattahi et al. 2015).

To increase the stability of 9-nitro camptothecin (9-NC), novel polymeric micelles encapsulating the drug were synthesized using cinnamic acid as the lipophilic moiety and mPEG as the hydrophilic block (Liang et al. 2013). The increase of lipophilic moiety in their micelles reduced the burst release effect of drugs from the micellar as well as enhanced the potency against liver cancer (Liang et al. 2013).

Docetaxel (DTX) is a member of taxane family and binds to tubulin, stabilizing spindle microtubules, and blocks mitosis (Bhalla 2003). In 2015, Hu and coworkers developed DTX-entrapped core-cross-linked polymeric micelles (CCL/DTX micelles) through covalent conjugation of DTX and CCL via hydrolysable ester bond to achieve sustained release of drug in vitro (Hu et al. 2015). The CCL consists of poly(ethylene glycol)-*b*-poly[N-(2-hydroxypropyl)methacrylamidelactate] (mPEG-*b*-p(HPMAm-Lac) copolymers. Single dose intravenous administration of CCL/DTX micelles (30, 60, or 125 mg/kg) demonstrated superior therapeutic efficacy in mice bearing MDA-MB-231 tumor xenografts compared to Taxotere®. Complete regression of tumor leading to 100% survival was observed for mice receiving single dosing of 125 mg/kg CCL/DTX micelles. This extraordinary efficacy could be perhaps explained by the enhanced accumulation of DTX, prolonged systemic circulation of CCL/DTX micelles, and suppression of angiogenesis (Hu et al. 2015). Treatment with CCL/DTX micelles reduced expression of

tumour stromal components such as pericytes, fibroblasts, and extracellularmatrix (collagen-1). These components are essential to contribute to increase in interstitial fluid pressure, tumor rigidity, and maturation of blood vessels in tumor microenvironment (Hu et al. 2015). Co-delivery of DTX and an autophagy inhibitor chloroquine (CQ) with enhanced drug stability, reduced toxic effect, and higher therapeutic efficacy was achieved using mixed micelles based on D-α-tocopherylpoly(ethylene glycol) (TPGS) and PEO–PPO–PCL with different length of hydrophobic chains (Shi et al. 2015). The size and drug loading of polymeric micelles was increased in conjunction with hydrophobicity of the copolymers. Irrespective of the hydrophobic chain lengths, the dual-drug-loaded PEO-PPO-PCL/TPGS micelles induced low hemolysis rate (<5%), exhibited sustained drug release and were significantly more effective than free DTX against MCF-7/ADR cells in vitro. Up to 190-fold decrease in IC_{50} were detected when cells were treated with drug-loaded micelles (Shi et al. 2015). Other recent findings have also demonstrated that the DTX delivery using polymeric micelles are suitable for treatment of metastatic and multidrug-resistant tumors (Li et al. 2014a, b, c).

Singh and coworkers recently developed transferrin-targeted novel polymeric micelles encapsulating DTX for enhanced treatment of lung cancer (Singh et al. 2016). The polymeric micelles were composed of poly(lactic acid)-D-α-tocopherylpoly(ethylene glycol) 1000 succinate (PLA-TPGS) and assembled with TPGS-Tf conjugate. The loading of DTX (39.69 ± 2.4 μg/mg) into micellar core was achieved using solvent displacement method. Unmodified PLA-TPGS/DTX micelles and PLA-TPGS-Tf/DTX micelles achieved approximately 7.7- and 70.34-folds decrease in IC_{50} value (stronger cytotoxicity) against A549 cell line compared with clinical Docel™ (Singh et al. 2016).

2.2 Polymeric Nanoparticles for Therapeutic Applications in Cancer

2.2.1 PTX-Loaded Polymericnano Particles

Several studies have shown that the encapsulation of PTX in PLGA nanoparticles improved the stability of the drug and anti-cancer activities compared to commercial Taxol® and free PTX (Yu et al. 2016; Averineni et al. 2012) (Tables 2 and 3). In a recent study, PTX-loaded PLGA nanoparticles with sizes ranging between 49 and 95 nm and alterable surface charges were produced via nanoprecipitation without the use of detergents (Le Broc-Ryckewaert et al. 2013). In the presence of serum, negatively charged PTX-loaded PLGA nanoparticles were relatively stable with slight increase in size. Meanwhile, for positively charged PTX-loaded PLGA nanoparticles, a serum effect which corresponds to altered size and zeta potential as a result of serum protein adsorption, occurred. PTX-loaded PLGA nanoparticles with positive charges were more cytotoxic against PC3 human prostate cancer cells compared to negatively charged nanoparticles. The authors have illustrated that positively charged nanoparticles had higher interaction with PC3 cells and tend to be localized in the cell membrane (Le Broc-Ryckewaert et al. 2013).

Table 2 Recent examples of polymeric nanoparticles as delivery vehicle for chemotherapeutic drugs

Polymeric material	Physicochemical properties (size, zeta potential)	Drug	Targeting cancer	Reference
Poly(butyl cyanoacrylate)	With poloxamer 188 stabilizer (246 nm, −23 mV); with dextran stabilizer (202 nm, −13.5 mV)	DOX	Glioblastoma	Petri et al. (2007)
Methoxy polyethylene glycol-poly (lactic-*co*-glycolic acid)	120–140 nm	DOX	Breast cancer	Alibolandi et al. (2015)
Methoxy polyethylene glycol-poly (caprolactone)	144 nm, −0.99 mV	Ursolic acid	Gastric cancer	Zhang et al. (2013a, b)
Chitosan-graft-D-α-tocopheryl polyethylene glycol	121–183 nm, 19.9–29.6 mV	DOX	Multidrug resistant liver and breast cancer	Guo et al. (2014)
Chitosan and β-glycerophosphate	23–24 nm, 0.03 to −14.1 mV	Cisplatin	Colon cancer	Abdel-Bar et al. (2016)
Polyethylene glycol-carboxymethylcellusose	118–134 nm	DTX	Prostate, breast, lung, pancreas cancer	Ernsting et al. (2011)
Polyethylene glycol-*b*-poly (D,L-lactide)	112 nm, neutral	Bortezomib	Triple negative breast cancer	Shen et al. (2015)
Poly(L-lysine)-carboxylate and hyaluronic acid	Depend on the ratio between carboxylic acid to primary amine: particle size range from 217-38,118 nm and zeta potential values range −23 to 0.36 mV	PTX and gemcitabine	Biliary cancer	Noh et al. (2015)
Poly(L-lactic acid) and Poly(L-lactic acid)-blend polyethylene glycol	283–294 nm	5-fluorouracil	Throat cancer	Mattos et al. (2016)
Poly(lactic-*co*-glycolic acid)	62–120 nm, −20.3 to −25.2 mV	5-fluorouracil and curcumin	Throat cancer	Masloub et al. (2016)
Poly(lactic-*co*-glycolic acid)	318 nm	PTX		

(continued)

Table 2 (continued)

Polymeric material	Physicochemical properties (size, zeta potential)	Drug	Targeting cancer	Reference
			Breast and cervix cancer	Jin et al. (2009)
Poly(lactic-*co*-glycolic acid)	133–160 nm, −23 to −33 mV	PTX	Lung cancer	Fonseca et al. (2002)
Poly(lactic-*co*-glycolic acid)	98.8 nm, −0.8 mV	Vincristine and verapamil	Drug-resistant breast cancer	Song et al. (2009)
Poly(lactic-*co*-glycolic acid)	250–280 nm, −17 to 19 mV	CPT	Colon cancer	Xiao et al. (2015a, b)
Poly(ethylene glycol)-poly(lactic-*co*-glycolic acid)	112–190 nm, 6.2–6.5 mV	PTX	Cervix cancer	Danhier et al. (2009)
Poly(lactic-*co*-glycolic acid)-D-α-tocopheryl polyethylene glycol	200–300 nm	PTX	Breast cancer	Zhao and Feng (2010)
Poly(lactic-*co*-glycolic acid)-D-α-tocopheryl polyethylene glycol	120 nm, −15 to −22 mV	PTX	Lung cancer	Sun et al. (2014a, b)
Mannitol-core-poly(D,L-lactic-*co*-glycolic acid)-D-α-tocopheryl polyethylene glycol	91–138 nm, −11 to −21 mV	DTX	Breast cancer	Tao et al. (2013)
Poly(L-lactide)-glycolic acid)-D-α-tocopheryl polyethylene glycol	130–270 nm	DOX	Drug-resistant breast cancer	Li et al. (2010)
Poly(ε-caprolactone)-D-α-tocopheryl polyethylene glycol	237 to 444 nm, −30 to −37 mV	PTX	Breast cancer	Bernabeu et al. (2014)
Poly(methyl methacrylate)	92 nm, −45 mV	Zinc (II) phthalocyanine	Leukimia cancer	Feuser et al. (2016)
Glycol chitosan	220–416 nm	PTX	Breast cancer	Kim et al. (2006)

Table 3 Examples of ligands targeted polymeric nanoparticles for active targeting of chemotherapeutic drugs

Type of ligands	Polymeric material	Physiochemical properties (size, zeta potential)	Drug	Targeted cells	Reference
Transferrin	Poly(lactic-*co*-glycolic acid)	93 nm, −11.3 mV	Methotrexate	Brain cancer	Jain et al. (2015)
Transferrin	Poly(lactic-*co*-glycolic acid)	187 nm, −17.3 mV	7α-(4′-amino) phenylthio-1,4-androstadiene-3,17-dione	Breast cancer	Zheng et al. (2010)
Peptide: RGD	PEGylated-poly(lactic-*co*-glycolic acid)	146 nm	PTX	Liver cancer	Danhier et al. (2009a, b, c)
Peptide: RGDfk	Polyglylutamic acid	7 nm	PTX	Brain cancer	Eldar-Boock et al. (2011)
Peptide: iNGR	Poly(ethylene glycol)-poly(lactic-*co*-glycolic acid)	127 nm, −18.6 mV	PTX	Brain cancer	Kang et al. (2014)
Peptide: LFC131	Chitosan	189 nm, −31 mV	DTX	Lung cancer	Wang et al. (2015a, b, c)
Peptide: LFC131	Poly(lactic-*co*-glycolic acid)	301 nm, −37 mV	DOX	Lung cancer	Chittasupho et al. (2014)
Peptide: Bombesin	Poly(lactic-*co*-glycolic acid)	111 nm, −26 mV	DTX	Breast cancer	Kulhari et al. (2014)
Peptide: low molecular weight protamine	Poly(lactic-*co*-glycolic acid)	Approximately 230 nm, +30 mV	DOX	Multidrug-resistant breast cancer	Wang et al. (2014)
Folate	Poly(ester-urethane) linked poly (ε-caprolactone) and polyethylene glycol	132 nm, −7.1 mV	DOX	Breast cancer	Kumar et al. (2015)
Folate	Chitosan-functionalized poly(lactic-*co*-glycolic acid)	206.9 nm, +21.7 mV	Bicalitamide	Prostate cancer	Dhas et al. (2015)

(continued)

Table 3 (continued)

Type of ligands	Polymeric material	Physiochemical properties (size, zeta potential)	Drug	Targeted cells	Reference
Folate	Gelatin	210 nm, −11.7 mV	Cisplatin	Cervix cancer	Dixit et al. (2015)
Folate and peptide	Poly(ethylene glycol)-poly(lactic-*co*-glycolic acid)	224–235 nm, −8.5 to −13 mV	Vincristine sulfate	Breast cancer	Chen et al. (2012)
Aptamer	Poly(ethylene glycol)-poly(lactic-*co*-glycolic acid)	156 nm, −32.9 mV	PTX	Brain cancer	Guo et al. (2011)
Epidermal growth factor	Gelatin	230 nm	Cisplatin	Lung cancer	Tseng et al. (2009)
Epidermal growth factor: anti-HER2	Poly (2-methyl-2-carboxytrimethylene carbonate-*co*-lactide) graft-poly (ethylene glycol)-furan	125 nm	DOX	Breast cancer	Shi et al. (2009)
Monoclonal antibody: Herceptin	Polyethylenimine and Poly(lactic-*co*-glycolic acid)	280 nm, 1 mV	PTX	Breast cancer	Yu et al. (2016)
Heparin	Gelatin	189 nm, −26.8 mV	Cisplatin	Breast cancer	Jain et al. (2012)
Bisphosphonate: alendronate	Poly(lactic-*co*-glycolic acid)	223–235 nm	Curcumin and bortezomib	Metastasis breast cancer	Thamake et al. (2012)
Bisphosphonate: alendronate	Poly(lactic-*co*-glycolic acid)	Approximately 180 nm	Cisplatine	Bone cancer	Yu et al. (2016)
Bisphosphonate: zoledronate	Poly(lactic-*co*-glycolic acid)	132 nm	DTX	Bone metastasis	Ramanlal Chaudhari et al. (2012)

In 2014, Gupta and coworkers described the synthesis of novel PLGA/poloxamer blend nanoparticles encapsulating PTX for intravenous administration using oil-in-water emulsion/solvent evaporation technique (Gupta et al. 2014). The spherical nanoparticles exhibited negative surface charge (−22.7 ± 5.7 mV) with particle size of 180 nm, stable without significant changes for three months and were non-hemolytic in vitro. The introduction of hydrophilic PEO chains of poloxamer acted as a steric barrier to prevent aggregation and adsorption of plasma protein onto the nanoparticle and subsequent clearance by phagocytic cells (Gupta et al. 2014). PTX-loaded PLGA/poloxamer blend nanoparticles showed significantly improved cytotoxicity against MCF-7 and colo-205 (human Caucasian colonadenocarcinoma cells). For example, PTX in the form of nanoparticles (IC_{50}: 0.53 nM) were approximately10-folds more cytotoxic toward Colo-205 compared to free PTX (IC_{50}: 5.34 nM) (Gupta et al. 2014). In another study, PTX blend nanoparticles consisting of poloxamer 188 and PCL were investigated to overcome MDR in a PTX-resistant human breast cancer cell line (MCF-7/TAX) (Zhang et al. 2010a, b). An increased internalization of PTX-loaded PCL/poloxamer nanoparticles by MCF-7/TAX was observed which was accompanied with stronger anti-cancer activity compared to Taxol® (IC_{50}: 0.65 μg/ml vs. 6.82 μg/ml) (Zhang et al. 2010a, b).

Using free radical dispersion polymerization to facilitate attachment of small molecules onto nanoparticles' surface, multifunctional PTX-loaded PLA-PEG nanoparticles with stealth properties were developed (Adesina et al. 2014). The long-circulating properties of spherical PTX-loaded PLA-PEG nanoparticles were confirmed using both qualitative and quantitative method. Through SEM observation, the nanoparticles were constructed from a lactide core and a corona of PEG. Quantitatively, complete PTX release from the nanoparticles was only observed after 7 days (Adesina et al. 2014). In vitro cytotoxicity data against breast and ovarian cancer cells suggested that the nanoparticle formulation had comparable effect with free PTX.

As mentioned earlier, PTX is an ideal chemotherapeutic agent as it could inhibit cell division via promoting the gathering and stabilization of microtubules. Owing to its intrinsic high hydrophobicity, PTX failed to penetrate the blood brain barrier (BBB) which in turn resulting in extremely low efficacy against brain tumor treatment.

To overcome this restriction, PTX has been encapsulated in mPEGylated PCL nanoparticles (Xin et al. 2010). The cytotoxicity effect of PTX-loaded mPEG-PCL nanoparticles against C6 cells was not significantly different compared to Taxol®, which could be attributable to the limited amount of PTX released from nanoparticles over incubation period (Xin et al. 2010). In vivo fluorescence imaging, however, revealed that mPEGylated nanoparticles displayed much stronger intensity in the brain of C6 bearing mice. The anti-glioblastoma activity evaluated with respect to survival of intracranial C6 bearing mice followed the decreasing trend: MPEG-PCL/PTX nanoparticles > PCL/PTX nanoparticles > saline ≈ Taxol®. The enhanced therapeutic activity of mPEGylated nanoparticle in vivo was based on the effect of passive tumor targeting and long-circulation time (Xin et al. 2010). In addition, PTX-loaded mPEG-PLA nanoparticles enhanced the chemo-radiotherapeutic efficacy against

non-small lung cancer cells (A549). Both in vitro clogenic assay and in vivo tumor survival assay demonstrated that PTX-loaded mPEG-PLA nanoparticles sensitized the tumor cells for radiation and simultaneous killing activities (Jung et al. 2012). Ranganath and coworkers proposed the use of novel submicron/nanoscale PLGA implants as delivery vehicle of PTX in the application of post-surgical local chemotherapy against glioblastoma (Ranganath et al. 2010). The authors have previously demonstrated that PLGA microfibers with the ratio of 50:50 showed promising potential for PTX delivery in vitro and in vivo (Ranganath and Wang 2008). It was postulated that better drug penetration into the brain could be achieved using electrospun PLGA 50:50 nanofibers (approximately 100 nm in size), hence increased local PTX bioavailability in vivo and superior anti-glioma activity (Ranganath et al. 2010). BALB/c nude mice with intracranial humanglioblastoma (U87 MG-luc2) randomized to receive implants of PLGA/PTX nanoparticles (10 mg/kg), placebo, and the intratumoral injection of Taxol® once a week (10 mg/kg). Enhanced PTX penetration into mice brain (up to 5 mm from implant site) was observed even after 42 days post-implantation and this was coupled with statistically significant tumor inhibition (30-folds) and low proliferation index (Ranganath et al. 2010).

2.2.2 DOX-Loaded Polymeric Nanoparticles

It is known that the site of action of DOX is within the nucleus. Therefore, nuclear localization signal (NLS) conjugated DOX/PLGA nanoparticles for intracellular trafficking within nucleus is a potentially effective drug delivery method for improved antitumor activity (Misra and Sahoo 2010). The NLS peptide was conjugated to the carboxylic group of the DOX/PLGA nanoparticles to yield relatively uniform particle size distribution (size: 226 nm and PI index: 0.15). Confocal observations revealed that the NLS conjugated DOX/PLGA nanoparticles were transported directly to nucleus of MCF-7 cells and acted as intracellular depot for prolonged DOX retention. This was reflected in the differences in IC_{50} values and G2/M arrest events for cells treated with NLS modified nanoparticles (2.3 μM, 60.2%) and free DOX (17.6 μM, 40.7%) (Misra and Sahoo 2010).

Another type of peptide with enzyme-sensitive feature, which ideally releases DOX at tumor site upon degradation by cathepsin B or papain, has been successfully developed recently (Yang et al. 2013). The enzyme-sensitive GFLG peptide was sandwiched between DOX and HPMA block copolymer in which the former was covalently bound to the peptide. Meanwhile, GFLG was introduced into the main chain of the copolymers with hydrophilic and hydrophobic blocks. The resultant MA-GFLG peptide-DOX nanoparticles exhibited significantly improvement in antitumor performance using 4T1 murine breast cancer model as evaluated using mice weight shifts, tumor growth curves, tumor growth inhibition, and immunohistochemical analyses (Yang et al. 2013). Owing to the high molecular weight of copolymer (90 kDa) coupled with enzymatic biodegradability characteristics, alteration of pharmacokinetics (prolonged blood circulation and accumulation) in conjunction with increased particles' stability in vivo was evident. The authors suggested that the presence of GFLG oligopeptide spacer, which is

susceptible to tumor-overexpressed lysosomal cysteine proteinase cathepsin B, provided additional stability in plasma and serum, altered microenvironment of tumor tissues and finally improved tumor suppression (Yang et al. 2013). A polyester-based hyperbranched dendritic-linear (HBDL)-based nanoparticles loaded with DOX was designed to overcome microsomal glutathione transferase 1 (MGST1)-mediated drug resistance in breast cancer cells (Zeng et al. 2014). HBDL/DOX nanoparticles was translocated across membrane of resistant cells via endocytic transport mechanisms involving macropinocytosis and clathrin-mediated endocytosis that are distinct from the uptake pathway of free DOX. In comparison, the internalization of free DOX is often via diffusion through the membrane where P-gp efflux pumps are located (Zeng et al. 2014).

2.2.3 Other Chemotherapeutic Drugs Loaded Polymericnano Particles

Tamoxifen (TAM), a nonsteroidal antiestrogen molecule, is used to treat patients with estrogen receptor (ER) positive breast cancer through inhibition of estradiol induced cell proliferation (Goetz et al. 2008). Oral therapy of TAM results in severe side effects such as oxidative stress mediated hepatotoxicity, hemolytic anemia, and possible high risk of endometrial cancer (Mocanu and Harrison 2004; Lee et al. 2010). Alternative nanoparticle-based drug delivery system to increase the bioavailability of TAM and reduced side effects to date include TAM/PCL nanoparticles, TAM/PLGA nanoparticles, TAM-loaded injectable microspheres or TAM-loaded alginate/chitosan nanoparticles. In a recent work, it was demonstrated that the presence of surfactants is crucial to obtain stable, non-aggregated TAM-loaded PLA nanoparticles with optimal loading efficiency and surface charges. The authors reported that the nanoparticle parameters were independent on the concentration of surfactants; rather influenced by the type of surfactant itself. For instance, PVA exhibited higher hydrophobic interactions and anti-aggregation properties compared to poloxamer-188 and polysorbate-80, hence promoted stronger steric stabilization in oil–water emulsion (Altmeyer et al. 2016). TAM-loaded PLA nanoparticles exhibited negligible hemolysis (independent of drug concentration or time of incubation) while maintaining the cytotoxicity over Hela cells. It was suggested that slow and prolonged TAM release from PLA nanoparticles is the reason causing low hemolytic potential and sustained cytotoxicity effect (Altmeyer et al. 2016). In vivo investigation on the effect of TAM-loaded PLA nanoparticles on DMBA induced mammary tumor in female Wistar rat showed marked reduction in both tumor size and hepatoxicity as compared to free TAM and control groups (Pandey et al. 2015). Simultaneous oral delivery of dual-drug-loaded PLGA nanoparticles (TAM and topotecan hydrochloride, TOP) was engineered to achieve synergistic effect in metastatic breast cancer treatment via enhancement of TOP permeation through the guts (Khuroo et al. 2014). Although both TAM and TOP act on DNA, their mechanism actions are different; hence synergistic action can be realized. The ability of TAM to inhibit P-gp like ABC transporters prevents the efflux of TOP and subsequently reduces the development of TOP resistance. These spherical TAM/TOP

loaded PLGA nanoparticles (average size: 150 nm) were highly lethal at small concentrations against MCF-7 cell lines compared to single or combination free drugs. Using ex vivo gut permeation study, the authors revealed that the cumulative TOP permeated from TAM/TOP nanoparticles showed a 2-fold increase compared to free TOP suspension alone (Khuroo et al. 2014).

Householder and coworkers have first reported an effective therapy of an intracranial gliomatumor with camptothecin (CPT)-loaded PLGA nanoparticles delivered using systemic route (Householder et al. 2015). CPT-loaded PLGA nanoparticles were more densely accumulated in the tumor core without exerting obvious adverse effect up to 20 days compared to healthy and peri-tumor brain regions. C57BL/6 albino mice bearing intracranial glioma tumor showed positive responses to the 119 nm-CPT nanoparticles in terms of retardation of tumor growth and mice survival (Householder et al. 2015). The median survival for mice receiving CPT nanoparticles, free-CPT, and saline were 36.5, 32, and 28 days, respectively (Householder et al. 2015). Hybrid cyclodextrin and chitosan nanoparticles encapsulating CPT intended for oral chemotherapy also resulted in enhanced drug permeability and anti-cancer activity (Unal et al. 2015). Both anionic and cationic CPT-hybrid nanoparticles, synthesized using wet nanoprecipitation method, had an average size of 187.5 and 204.2 nm, respectively, and were stable in both gastric and intestinal environments (i.e., minimal changes of size and zeta potential) (Unal et al. 2015). In another study, a series of cationic chitosan-functionalized polymeric nanoparticles (193–224 nm) were employed as co-delivery vehicles of CPT and CUR for effective colon cancer therapy (Xiao et al. 2015a, b). The cationic CPT/CUR nanoparticles exhibited clear synergistic patterns against colon-26 cells and the effect was drug ratio-dependent with CPT/CUR ratio of 4:1 being the most cytotoxic (Xiao et al. 2015a, b).

3 Stimuli-responsive Polymeric Nanocarriers

3.1 Endogenous Stimuli-responsive Polymeric Nanoparticles and Micelles

Stimuli-responsive polymeric micelles are a class of polymers that undergoes structural changes in response to both intrinsic and external stimuli for applications such as controlled drug release, enhanced internalization, and controlling the intracellular drug fate on the surrounding tumor tissue. The intrinsic stimuli in tumor microenvironment include pH, redox potential, and temperature (Mura et al. 2013). Among the different intrinsic stimuli in tumor microenvironments, the incorporation of a pH-triggered mechanism is the most common for delivery of various chemotherapeutic drugs such as DOX, PTX, DTX, and gemcitabine (GCT) (Scheeren et al. 2016; Zhao et al. 2012, 2013). Comprehensive reviews on the strategies used to design pH-responsive micelles and nanoparticles have been

published elsewhere (Biswas et al. 2016; Liu et al. 2014; Gao et al. 2013; Mura et al. 2013).

Tumor tissues possess lower extracellular pH (pH_e) compared to normal tissues as a result of excessive accumulation of lactic acid via anaerobic glycolysis. It should be noted the only subtle differences in pH exist between healthy tissues ($\sim$7.4) and the extracellular environment of solid tumors (6.5–7.2) (Engin et al. 1995). Acidic microenvironment benefits the survival of tumor cells because it slows down the internalization of basic drugs; hence, leading to reduced anti-cancer efficacy and higher tumor angiogenesis. Therefore, an effective pH-responsive nanosystem should demonstrate obvious signals to any slight changes in extracellular pH of tumor microenvironment. The exploitation of acidic pH as drug-release trigger can be loosely categorized into three strategies; (i) pH-responsive nanoparticles for rapid drug release; (ii) pH-responsive nanoparticles for cellular targeting and internalization; and (iii) pH-responsive nanoparticles for intracellular cytosolic drug release (Table 4; Fig. 2). Many studies have explored the use of amphiphilic copolymers with ionizable groups with higher solubility in acidic conditions (Bae et al. 2005). Anionic polymers with carboxyl groups such as poly (acrylic acid) (PAA), and poly(methacrylic acid) (PMA) most commonly used for this purpose (Biswas et al. 2016). Other pH-responsive polymers are polymers with sulfonamide groups or poly(amino acids) consisting of carboxylic acid group in the side chains (Biswas et al. 2016). Another method to incorporate pH-sensitive feature is via conjugation of polymeric systems (diblock, triblocketc) with acid-labile bonds (i.e., hydrazone, oxime, or acetals) in which the cleavage releases the chemotherapeutic drugs either encapsulated within the core of micelles or anchored on the polymer (Zhu et al. 2012; Jin et al. 2011; Du et al. 2012; Deng et al. 2015). Incorporating targeting ligands and altering surface charges of polymer (i.e., amine-containing polymers) have been used as well to escape endosomal compartment within cells (Zhang et al. 2012a, b; Kim et al. 2008).

In this context, Xu and coworkers had published an article on how to design and predict drug release in pH-responsive polymeric micelles (Xu et al. 2012). By employing citraconic amide as pH-sensitive precursor, Cao and coworkers have designed mPEG-pH-PCL and non-pH-sensitivemPEG-CA-PCL micelles to deliver DOX to treat HepG2 and 4T1 cell lines (Cao et al. 2014). The in vitro release study of DOX revealed that mPEG-pH-PCL has higher DOX release compared to mPEG-CA-PCL at acidic condition (pH 5.5), but the release rates were comparable at physiological condition (pH 7.4). Cell viability (IC_{50}) of HepG2 and 4T1 cell lines were more significantly affected when treated with loaded mPEG-pH-PCL/DOX compared to mPEG-CA-PCL/DOX micelles. However, 4T1 cell line was more susceptible to mPEG-pH-PCL/DOX micelles compared to HepG2 which was an indirect indication suggesting the variation of sensitivity of cancer cells of different origin (Cao et al. 2014). In addition Lee and coworkers have developed pH-sensitive poly(L-histidine) (PHis)-based loaded with DOX micelles specifically for targeting acidic tumor microenvironment (Lee et al. 2003). PHis has a pH-dependent solubility behavior in which its unsaturated nitrogen of imidazole ring is protonated at low pH (Lee et al. 2003; Gao et al. 2005a, b). As a

Table 4 Examples of pH-responsive polymeric micelles for delivery of chemotherapeutic drugs

Polymeric materials	Drug	Cancer cell line	Remarks	Reference
Poly(2-ethyl-2-oxazoline)	DOX	MCF-7	DOX-loaded polymeric micelles via conjugation exhibited lower IC_{50} values compared to free DOX. DOX-loaded micelles were present in nucleus and cytoplasm of cells The reduction of tumor volume on MCF-7 bearing athymic nude mice followed the decreasing order: Conjugated DOX-loaded micelles (72.4%) > free DOX (62.3%) (45.5%) > chemically bound DOX to polymer	(Li et al. 2015a, b, c, d, e)
PEGylated glucolipid-like conjugate with chitosan and stearic (CS) acid [PCCS]	DOX	BRL-3A and BEL-7402	Up to 87% of DOX was encapsulated into PCCS micelles. The release of DOX was more than 70% of DOX within 48 h at pH 5.0 pH-responsive PCCS/DOX micelles increased the cytotoxicity effect toward BEL-7402 by 2–3 fold compared to non-pH-responsive micelles (PCS) Due to the higher cellular uptake of PCCS/DOX micelles compared to PCS/DOX micelles and free DOX in tumor tissue, PCCS formulation was more effective to inhibit tumor growth and simultaneously reduced toxicity effect against tumor-bearing mice	Hu et al. (2012)

(continued)

Table 4 (continued)

Polymeric materials	Drug	Cancer cell line	Remarks	Reference
Poly(β-amino ester)-poly(ethylene glycol) [RPAE-PEG]	DOX	HepG2	The release rate of DOX was higher in acidic buffer (pH 6.5) compared to pH 7.4. The presence of DTT (reducing agent) triggered more DOX release at pH 6.5. RPAE-PEG/DOX micelles were rapidly internalized via endocytosis and exerted stronger cytotoxicity against HepG2 cells than free DOX	Chen et al. (2011)
Poly(ethylene oxide)-block-poly(ε-caprolactone) [PEO-*b*-PCL]	DOX and multidrug resistant (MDR)-1 siRNA	MDA-MB-435	Significantcellular uptake, improved DOX penetrationinto nucleus, and enhanced DOX cytotoxicity in DOX-resistant cells was demonstrated by the polymeric micelles harboring cell membrane translocation (cell penetrating TAT), pH-triggered (via hydrazone linkage) drug release and cancer therapeutics (DOX and siRNA) properties	Xiong and Lavasanifar (2011)
Polysialic acid	PTX	SGC-7901	More than 40% of PTX was released in mild acidic condition (pH 5.0) after 72 h of incubation. Although PTX-loaded micelles 53.8% of cell viability) was weaker than free PTX (35.3% of cell viability) in terms of cytotoxicity, but the micellar formulation was highly stable at physiological condition	Zhang et al. (2016a, b)
Methoxy poly(ethylene glycol)-poly(ε-caprolactone) (mPEG-PCL)	DTX	MCF-7/A, MCF-7 and A549	mPEG-PCL/DTX micelles exerted negligible hemolytic effect and higher cancer killing effect irrespective of concentration and treatment time	Zhang et al. (2016a, b)

(continued)

Table 4 (continued)

Polymeric materials	Drug	Cancer cell line	Remarks	Reference
Poly(ethylene glycol)-poly(L-histidine)-poly(D,L-lactide-*co*-glycolide) (PEG-pHis-PLGA) and D-α-tocopheryl polyethylene glycol 1000 (TPGS) (mixed micelles)	Gambogic acid (GA)	Drug-sensitive human breast MCF-7 and drug-resistant MCF-7/ADR cells	GA-loaded micelles improved the toxicity effect on both MCF-7 and MCF-7/ADR cell lines. More than 50% of apoptotic cells in MCF-7/ADR were observed when treated with GA-loaded mixed micelles. The caspase 3/7 activities and cleaved PARP level were significantly higher when the resistant cells were treated with GA-loaded mix micelles compared to free GA. This mixed formulation also effectively reduced the expression of anti-apoptotic proteins Bcl-2 and survivin	Wang et al. (2015a, b, c)
N-benzyl-*N*,*O*-succinyl chitosan (BSCS)	Curcumin (CUR)	HeLa, SiHa and C33a	CUR encapsulated in chitosan micelles was stable up to four months. The IC_{50} of CUR/chitosan micelles were 4.7, 3.6, and 12.2 folds lower than free CUR against HeLa, SiHa and C33 cell lines, respectively. In addition, higher apoptosis levels were observed in these three cell lines when treated with chitosan/CUR micelles	Sajomsang et al. (2014)
mPEG-*b*-polycarbonate	DOX	HepG2, HEK293, 4T1	Mussel-inspired copolymer design with catechol side chain for covalent conjunction of DOX to acid-sensitive linker (*p*-quinoneimines) was developed. Self-assembled mPEG-polycarbonate/DOX micelles were kinetically stable, released drug via	Chan et al. (2016)

(continued)

Table 4 (continued)

Polymeric materials	Drug	Cancer cell line	Remarks	Reference
			pH-triggered intracellular mechanism and possessed comparable toxicity to free DOX in vitro In vivo efficacy of DOX-loaded micelles was significantly higher than free DOX	
PEG	DOX	HEK-293, HeLa, 4T1	Micelles consisted of shell-forming PEG and core-forming DOX covalently conjunction through acid-sensitive hydrazone bonds to the sidechains of the norbornene block. In aqueous conditions, the block copolymer self-assembled into spherical nanostructure with well-shielded drug moieties. The micelles were capable to control intracellular environment-sensitive drug release and enhanced DOX delivery	Rao et al. (2012)
methoxy poly(ethylene glycol)-*b*-poly(ε-caprolactone-*co*-γ-dimethyl maleamidic acid-ε-caprolactone) mPEG-*b*-PCL	DOX	HepG2	PEG-*b*-PCL copolymer micelles exhibited pH-responsive characteristics by harboring different amount of acid-labile β-carboxylic amides on the polyester moiety Hydrolysis of β-carboxylic amides in acidic conditions rapidly released DOX and triggered higher cellular uptake via electrostatic endocytosis. IC_{50} values for free DOX and DOX-loaded micelles were 0.49 and 0.62 μg/ml, respectively	Deng et al. (2014)

(continued)

Table 4 (continued)

Polymeric materials	Drug	Cancer cell line	Remarks	Reference
D-α-Tocopheryl Polyethylene Glycol Succinate-Poly(β-amino ester) TPGS-*b*-PBAE	DTX	Drug-sensitive human ovarian A2780 and drug-resistant A2780/T cells	DTX-loaded TPGS-*b*-PBAE micelles possessed the ability to overcome multidrug resistance by the synergistic effect of the pH-sensitive behavior (PBAE) and P-gp inhibition (TPGS) The IC50 of DTX-loaded micelles were 100-fold lower than commercial DTX in against A2780/T cells	Zhao et al. (2013)
1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol DSPE-PEG	PTX	4T1	pH-responsive and rapid intracellular (endosomal) drug release of DSPE-PEG-based micellar system was achieved through introduction of antinucleosome antibody (mAb 2C5) and poly(l-histidine) (PHIS). Up to 95% PTX was released within 2 h at pH around 5.5 PTX-loaded micelles were more effective against 4T1 cells at acidic conditions b (pH 5.8 versus pH 7.4)	Wu et al. (2013)
Styrene-maleic acid (SMA)	Cisplatin	HeLa	A high-loading, water-soluble cisplatin-polymer complex was developed by formation of ionic complex with dicarboxylate residues of maleylgroups in the SMA chain Higher accumulation of SMA/cisplatin was found in tumor tissue after 24 h of intravenous administration compared to free cisplatin	Saisyo et al. (2016)

(continued)

Table 4 (continued)

Polymeric materials	Drug	Cancer cell line	Remarks	Reference
Stearoyl–PEG–poly-sulfadimethoxine methacrylate stearoyl–PEG–polySDM	PTX	MCF-7	PTX loading was 3.25 ± 0.25% (w/w%). The PTX-loaded micelles were stable at pH 7.4 and rapidly aggregated at pH 6.5 to release PTX, thus resulted in higher degree of association with cells	Ravazzolo et al. (2013)
poly(cholesteryl acrylate-*co*-methoxypoly(ethylene glycol) methacrylate) poly(CHOLy-*co*-mPEG)	CPT	MCF-7, HeLa	Sustained release of drug was triggered by hydrolysis of the ester linkages in acidic conditions. CPT-loaded micelles were non-hemolytic and could easily permeate into both MCF-7 and HeLa cells	Laskar et al. (2014)

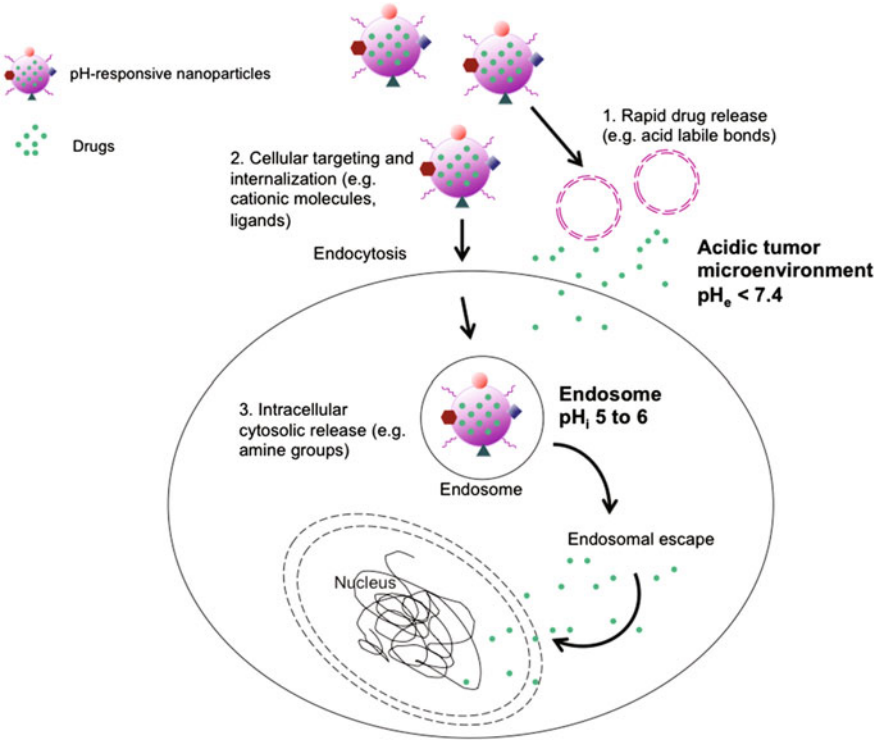


Fig. 2 Schematic diagram demonstrating the common strategies to exploit acidic tumor microenvironment as drug release trigger for pH-responsive nanoparticle systems

consequence, the destabilization of PHis-based micelles caused the higher DOX release rate at pH lower than 7.0. When A2780 cells were cultured with PHis-PEG/DOX micelles at different pH conditions (6.8, 7.4 and 8.0), higher intracellular DOX concentration was detected in acidic conditions (Lee et al. 2003). The authors believed that the rapid dissolution of DOX from polymeric micelles coupled with the stealth properties of PEG, the retention and availability of DOX was much increased compared to free DOX (Lee et al. 2003). PTX-loaded pH-sensitive polymeric micelles could be effectively delivered to prostate cancer cell lines (PC-3 and 4T1.2) as reported by Zhang and coworkers (Zhang et al. 2015). Besides the promotion of PAX release in acidic condition, the authors demonstrated that the regulation of carbon chain and different electron-withdrawing groups via stearic environments around the hydrazone linker modulated the pH sensitivity level of micelles (Zhang et al. 2015).

Nanoparticles with high DOX loading and pH-responsive behavior were synthesized through nanoprecipitation of DOX-polymer conjugate (Yu et al. 2014). The PLA-*g*-DOX nanoparticles was prepared using multistep reactions: (i) azide–alkyne click reactions to transform acetylene-functionalized PLA into PLA-*graft*-aldehyde (PLA-*g*-ALD); (ii) conjugation of amine functionality of DOX to ALD backbone of

PLA-*g*-ALD via acid-labile linker; and (iii) nanoprecipitation of graftedPLA-*g*-DOX in water containing distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[maleimide-PEG2000] (DSPE-PEG-MAL) (Yu et al. 2014). The resultant PLA-*g*-DOX nanoparticles were spherical, negatively charged, and high colloidal stability without noticeable aggregation in serum media. More than 3-folds increase of DOX release from PLA-*g*-DOX was achieved at pH 5.5. Irrespective of different concentration of DOX, PLA-*g*-DOX NP was the most potent to kill MCF-7 (Yu et al. 2014).

Two different compositions of shell cross-linked micelles (SCLM): SCLM-50 and SCLM-100 to deliver cabazitaxel (CTX) were developed for prostate cancer treatment (Aydin et al. 2016). Both prostate cell lines (PC-3 and C4-2B) were more sensitive toward SCLM-50/CTX micelles and non-shell cross-linked/CTX (NSCLM/CTX) micelles compared to free-CTX and SCLM-100/CTX micelles. This was contributed to the difference in uptake efficiency of these prostate cancer cell lines. It should be noted that the void micelles were nontoxic to HEK 293 cells (human embryonic kidney cells) even at high concentrations (50–100 folds higher than IC_{50} of CTX). Interestingly, the micelles formulation has lower recognition and uptake by macrophage (less than 10% of internalization) after exposure to serum proteins; thus suggesting that this micellar formulation could be ideal CTX delivery in regard to prostate cancer treatment (Aydin et al. 2016).

A star-shaped pH-sensitive polymeric nanoparticle based on [tetra-(methoxy-poly(ethylene glycol)-poly(2-(*N*,*N*-diaethylamino)ethyl methacrylate)-poly(ε-caprolactone) pentaerythritol) [mPEG-pDEA-PCL)4-PET], PDCP was developed for rapid PTX release and simultaneous prolonged blood circulation and rapid drug (Li et al. 2015a, b, c, d, e). Surprisingly, the cytotoxicity effect on MCF-7 cell lines and antitumor effect on in vivo mice model were nonstatistically different between free PTX and PTX-loaded PDCP. However, the tolerability and survival of mice toward PDCP nanoparticles was higher compared to free PTX solutions as demonstrated in increase body weight over time (Li et al. 2015a, b, c, d, e).

A pH-sensitive drug nanocarrier based on poly(styrene-*co*-maleic acid) [PSMAC]/PTX nanoparticles with accelerated drug release at pH mimicking lysosomes (pH 4.2) have been reported recently (Dalela et al. 2015). The maleic moiety of PSMAC was conjugated to PTX via ester linkage, using dicyclohexyl-carbodiimde (DCC) and 4-dimethylaminopyridine (DMAP). The conjugated PSMAC/DOX assembled into nanoparticles ranging from 165 to 185 nm in aqueous condition with negative surface charges (−22.2 mV). The longer incubation period of PSMAC/PTX nanoparticles in various cancer cell lines (MCF-7, MDA-MB 231, A549, HeLa, SKHEP 1 HepG2, CHO-K1, and L929) resulted in higher potency owing to slow, but sustained release of available PTX (Dalela et al. 2015). For determination of in vivo antitumor efficacy, weekly, multidosing regimen of either PSMAC/PTX (60 and 80 mg/kg), Taxol® (20 mg/kg) or saline (as control) were administered intravenously to Ehrlich Ascites Tumor (EAT)-bearing BALB/c syngenic mice. At day-15 of posttreatment, the tumor volume for mice receiving saline, Taxol®, PSMAC/PTX (60 mg/kg) and PSMAC/PTX (80 mg/kg) were 151, 103.6, 85.2, and 72.3 mm^3, respectively. At the completion of dosing regimen, the treatment with PSMAC/PTX (80 mg/kg) showed complete tumor

regression with no recurrence. The apoptotic index, measured in terms of caspase three activity, for PSMAC/PTX (80 mg/kg), PSMAC/PTX (60 mg/kg), Taxol®, and control (saline) was 1.88, 1.53, 0.79, and 0.11%, respectively. It should be noted that survival rate was significantly higher for PSMAC/PTX nanoparticles-treated group (64–87%) compared to that of Taxol® (49%) (Dalela et al. 2015).

To increase the internalization of drugs, functionalization of nanocarriers with cationic molecules could be employed. The cationic micelles are electrostatically attracted to negatively charged cell membrane followed by electrostatic-adsorptive endocytosis. A series of cationic poly(dimethysiloxane)-poly(2-(dimethylamino) ethyl methacrylate) [PDMS-*b*-PDMAEMA] block copolymer micelles with different molecular weight (M_w) of PDMAEMA was synthesized to deliver DOX intracellularly into HeLa cell line (Car et al. 2014). The cytotoxicity of HeLa cells was directly correlated to the M_w of PDMAEMA, which was due to higher degrees of association between cells' surface (negative charge) and PDMAEMA micelles (positive charge). The authors showed that PDMS-*b*-PDMAEMA/DOX micelles responded to intracellular pH changes via increased DOX release in acidic pH and were internalized through endocytosis to acidic cell compartments. The confocal images further supported the toxicity of PDMS-*b*-PDMAEMA/DOX micelles at late stage of incubation, whereby cell morphology changes and apoptotic cells were observed (Car et al. 2014).

A novel cRGDyK peptide modified pH-responsive nanoparticle based on poly (ethylene glycol)-poly(2,4,6-trimethoxy benzylidenepentaerythritol carbonate) [PEG-PTMBPEC] diblock copolymer loaded DOX was synthesized to kill tumor and inhibit angiogenesis simultaneously (Qiu et al. 2016). Modified DOX-loaded nanoparticles were more pronounced against B16 and HUVEC cell lines. The higher toxicity in both cell lines was correlated to the higher uptake modified DOX-loaded nanoparticles via receptor-mediated endocytosis and acidic-triggered drug release within the cells (Qiu et al. 2016).

The pH gradient, which exploits the acidified endosome and fusion with lysosome within cells, is gaining attention for intracellular drug release. Nanocarriers that disassemble or swell to achieve alterable drug release behavior in endosomal pH conditions (pH 5–6) have been designed via decoration with acid-sensitive bonds in the polymer backbone and acid-protecting groups, respectively. Recently copolymers of poly-l-lysine, P(bAE), and P(His) have been widely used to protect chemotherapeutic drugs from harsh endosomal–lysosomal environment (low pH and high enzymatic activity). In a study by Zhu and coworkers, lysosomal targeting polymeric micelles loaded with analog gemcitabine (GemC18) showed stronger antitumor activity against melanoma in both melanoma in vitro and in vivo conditions (Zhu et al. 2012). This activity was much pronounced when acid-responsive polymer was introduced owing to the higher hydrolysis rate of GemC18 to active GEM by lysosomal enzymes such as cathepsin B and D (Zhu et al. 2012). In a separate study, cross-linkers with different functionality (acid degradable and nondegradable) were used to prepare CPT-loaded micelles to target ovarian cancer (Huynh et al. 2012). Cellular uptake and release rate of CPT by OVCAR-3 cells were significantly varied in both micelles with and without the acid cross-linkers.

The conjugation of PCT micelles to acid cross-linker (2,2′-(propane-2,2-diylbis (oxy)) diethamine resulted in higher CPT release irrespective of the pH microenvironments. Owing to the pH-sensitive characteristic, acid cross-linked polymeric micelles were more toxic toward OVCAR-3 cells as a result of enhanced internalization using endocytosis and passive diffusion pathway (Huynh et al. 2012).

As mentioned earlier, the concept of endosomal pH targeting is based on the exploitation of differences of extracellular pH in tumor tissues and healthy tissues. A pH-responsive, poly(β-amino ester) [PbAE] nanoparticle which undergoes rapid dissolution in acidic microenvironment, was employed for PTX delivery to treat Jurkat acute lymphoblast leukimia T-cells (Lundberg 2011). The effectiveness of PbAE/DOX nanoparticles at lower concentration compared to non-pH-responsive PCL/DOX nanoparticles was attributable to higher intracellular DOX content in cytosol after ingestion of particles (pH-triggered dissolution of PbAE polymer in acidic endosomal-lysosomal compartment) (Lundberg 2011).

The exploitation of redox sensitivity owing to the differences in glutathione (GSH) concentrations and their affinity to cleave disulfide bonds is another strategy to trigger cytosolic release of drugs. Glutathione (GSH) is a thiol containing tripeptide, which is responsible for the reduction of disulfide linkages in cytoplasm. The intracellular cytosolic GSH concentrations (2–10 mM) are almost 1000-folds higher than extracellular GSH concentrations in physiological body fluids (2–10 μM)(Jia et al. 2014). Compared to healthy tissue, the levels of GSH are 4-fold higher which is attributable to drug resistance mechanism in cancer cells via GSH-mediated phase detoxification (Lale et al. 2015; Cheng et al. 2013; Biswas et al. 2016). Theoretically, polymeric micelles or nanoparticles carrying disulfide bonds are stable and could only be triggered to release drugs within cytosolic of cancer cells (high internal GSH). Disulfide bonds are generally linked between hydrophobic and hydrophilic domains in the amphiphilic block copolymers or conjugated to hydrophobic backbone of copolymer (Liu and Liu 2015; Wen et al. 2011; Zhang et al. 2013a, b; Sun et al. 2010; Li et al. 2012). In addition, GSH-sensitive agents could be cross-linked to the shell of micelles, leading to rapid disassembly of micelles and intracellular drug release inside the cells (Liu and Liu 2015; Samarajeewa et al. 2013).

A redox-sensitive poly(ethylene glycol)-poly(lactic acid) [MPEG-SS-PLA] loaded with PTX was synthesized using optimized oil-in-water emulsion/solvent evaporation to treat various cancer cell lines (A549, MCF-7 and HeLa) (Song et al. 2011). Multistep reactions were employed to synthesize MPEG-SS-PLA with disulfide linker between MPEG and PLA. The optimization of solvent, copolymer concentration, ratio of solvent to water produced MPEG-SS-PLA/PTX nanoparticles with rice-shaped like morphologies. The mean particle major axis length and minor axis length were 373.9 ± 4.8 nm and 129.5 ± 3.8 nm, respectively. Almost 90% of PTX was released from the nanoparticle in conditions with high intracellular GSH concentration. The PTX levels in the serum were almost negligible. Using standard MTT assay, PEG-SS-PLA/PTX nanoparticles exhibited the highest toxicity toward all three cell lines (Song et al. 2011). A novel pH-redox responsive micelle system that disintegrates in acidic conditions and exposes nitroxide radicals was effective to

enhance antitumor activity of DOX. This effect was due to the ROS scavenging activity of the released nitroxide radicals. The nitroxide radical-containing nanocarrier was a core-shell type of self-assembling polymeric micelles, with average diameter of 40 nm, consisting of poly(ethylene glycol-*b*-poly[4-(2,2,6,6-tetramethylpiperidine-*N*-oxyl)aminomethylstyrene] (PEG-*b*-PMNT) (Yoshitomi et al. 2013). The intravenous administration of radical-containing micelles at dosage of 100 mg/kg was found to decrease the ROS levels and TNF-α expressions. The cardiotoxicity effect of DOX was also reduced in vivo when colon-26 tumor bearing mice were pretreated with radical-containing micelles (Yoshitomi et al. 2013).

3.2 Exogenous Stimuli-Responsive Polymeric Nanoparticles and Micelles

Temperature-responsive drug delivery is one of the most studied strategies in particular for oncology as local tumor site demonstrate distinct hyperthermia (40–42 °C). An ideal temperature-responsive carrier should retain the drug load at normal body temperature (37 °C) and rapidly release the drug in heated pathological area. To date thermo-responsive liposomes are the most studied temperature-responsive carriers as demonstrated in several clinical trials. For polymeric micelles or nanoparticles, thermo-responsive polymers consist of temperature-responsive hydrophilic segments and a suitable hydrophobic segment. Such polymers are fully soluble below a certain temperature, more commonly known as lower critical solution temperature (LCST), via formation of hydrogen bond in aqueous conditions. Above the LCST, the disruption between hydrogen bonds of water and the polymer chains induce phase separation and precipitation in polymers, and subsequently destabilization of micelles. Various preferred polymers building blocks for temperature-responsive polymeric micelles or nanoparticles include poly(*N*-isopropyl acrylamide), PNIPAAM, poly(γ-2-(2-(2-methoxyethoxy)-ethoxy)ethoxy-ε-caprolactone)-*b*-poly(γ-octyloxy-ε-caprolactone). The LCST of PNIPAAM can be adjusted to slightly above physiological temperature for cancer applications through introduction of hydrophilic segments (Takeda et al. 2004; Biswas et al. 2016). For instance, copolymers of P(NIPAAM-*co*-acrylamide)-poly (lactide) and P(NIPAAM-*co*-*N*,*N*-dimethylacrylamide) poly(lactide) have LCST of 41 °C (Biswas et al. 2016; Nakayama et al. 2014). DTX-loaded PLA-conjugated PNIPAAM-based acrylamide showed thermo-responsive behavior by releasing high amount of drugs in hyperthermia condition (Liu et al. 2008). Significantly higher antitumor efficacy was observed in mice treated with thermo-responsive DTX-loaded micelles compared with the conventional DTX formulation (Liu et al. 2008). Hennink and coworkers reported the development of thermo-responsive PTX-loaded polymeric micelles based on pHPMAmDL-*b*-PEG block copolymers and evaluated the cytotoxicity, stability, and drug release kinetics in vitro (Soga et al. 2005).

Ultrasound-triggered drug delivery is effective to achieve spatiotemporal control of drug release at specific locations without exerting too much harmful effects on healthy tissues. Other attractive features of ultrasound-based delivery include noninvasive, zero ionizing radiations, and ease of tissue penetration depth by mere regulation of frequency, duty cycle, and time exposures. Both thermal and mechanical effect generated by radiation forces induced instability of polymeric micelles and subsequently triggered the release of drugs. Drug-loaded polymeric micelles coupled with ultrasound therapy could promote anti-cancer treatment via inducing thermal effects, enhanced drug diffusion into tumor region, and increase intracellular drug bioavailability. Gao and coworkers have developed mixed micelles of PEG-PLLA and PEG-PEG for encapsulation of DOX and perfluoropentane (PFP) (ultrasound imaging contrast agent) (Gao et al. 2008). The emulsion nanodroplets were formed by PFP and stabilized by PEG-PLLA and PEG-PEG polymeric micelles. As the boiling point of PFP was low (29 °C), at physiological temperatures the evaporation of PFP converted the nanodroplets into nanobubbles. Meanwhile, DOX was localized within the nanobubbles' wall. The authors showed that PFP/DOX-loaded micelles underwent conversion to nanobubbles in vivo, followed by coalescence into larger echogenic microbubbles and accumulated in tumor tissue via EPR effect (Gao et al. 2008). In another study, DOX-loaded perfluorocarbon (PFC)/mPEG-PLGA nanodroplets which could be transformed into nanobubbles at 37 °C showed higher rate of tumor inhibition (Du et al. 2011). The ultrasound-triggered drug release when sonicated for 0.5 min at 37 °C was pH-dependent whereby up to 9.59% DOX was released at pH 6.5 compared to that of pH 7.4 (2.22%). In vivo tumor reduction for mice receiving receiving DOX-loaded PFC/mPEG-PLGA nanodroplets coupled with ultrasound was 84.3% compared to 60.4% when ultrasound was not applied (Du et al. 2011). This approach was further proven to be versatile in delivering other chemotherapeutic drugs such as PTX and curcumin (Ji et al. 2014; Wan et al. 2012).

In another study, the intracellular accumulation of DOX/Pluronic 105 micelles was higher in HL-60, A2780, A2780/ADR, and MCF-7 cell lines when high frequency ultrasound was applied and this effect was correlated to the increase of membrane permeability of cells (Marin et al. 2002). Similar observation was also reported by Wan and coworkers in which the PTX uptake and subsequently cytotoxicity effect on drug-sensitive (MDCKII and MCF-7) and P-gp expressing cell lines (MDCKII-MDR and NCI-ADR) was enhanced by twofold in conjunction with ultrasound therapy (Wan et al. 2012). The expressions of P-gp, MRP, and lung resistance protein in HepG2/ADM were drastically reduced with the combination therapy of DOX-loaded polymeric micelles and ultrasound therapy (Gao et al. 2005a, b). In addition, the application of ultrasound is not only to attenuate the expression MDR proteins, it induced higher apoptotic level in HepG2/ADM cells (Wu et al. 2011). Park and coworkers have developed a multifunctional DOX-loaded PLGA-gold nanoparticles, which could trigger the release of DOX upon exposure to near infrared (NIR) (Park et al. 2009). Using HeLa cells as cytotoxicity model, higher therapeutic effect was obtained with PLGA-gold/DOX nanoparticles compared to monotherapy (Park et al. 2009).

3.3 Multiple Stimuli-Responsive Polymeric Nanoparticles and Micelles

Dual function polymeric micelles were developed to further improve the targeting delivery of DOX for cancer treatment (Chen et al. 2013a, b). Thermo-sensitive and pH-dependent polymeric micelles coupled with pH-sensitive phase transitions at mild acidic pH and body temperature were fabricated by functionalizing PEG-PCL copolymers using 6-aminocaproic acid (ACA) (Chen et al. 2013a, b). The ACA-PEG-PCL copolymers self-assembled into nanomicelles (66–75 nm) and could be triggered to release DOX in response to pH and temperature variation. For instance, to achieve 30% release of DOX, at least 70 h of incubation was required in neutral pH at 37 °C. However, ACA-PEG-PCL/DOX micelles released the same amount of DOX in acidic condition after incubation for 6 h. Using a tumor xenograft mice model with melanoma (MDA-MB-435), the tumor reduction activities after 32 days of drug administration followed the following decreasing trend: ACA-PEG-PCL/DOX micelles > free DOX > PEG-PCL/DOX micelles > empty micelles. The ratio of tumor size in mice normalized against untreated mice for ACA-PEG-PCL/DOX micelles, PEG-PCL/DOX micelles, and free DOX were 0.12, 0.72, and 0.38, respectively. In addition, side effects of DOX were also minimized, as the average body weight loss of mice was less than 5% (Chen et al. 2013a, b).

Kashyap and coworkers have designed dual thermo- and enzyme-responsive micelles consisting of 3-pentadecylphenol and oligoethylene glycol acrylate amphiphilic copolymers for DOX delivery to MCF-7 and HeLa cell lines (Kashyap et al. 2016). Hydrophobic acrylate monomer from 3-pentadecylphenol (PDP) was copolymerized tooligoethylene glycol acrylate (hydrophilic segment) via radical and RAFT methodologies to produce novel amphiphilic copolymers with thermo- and enzyme- responsive features. In water, the amphiphilic copolymers self-assembled into core-shell nanoparticle and had higher affinity toward DOX (loading of 3.78%). Significant differences in DOX release from the loaded micelles could be seen at 37 °C (normal body temperature) and 43 °C (cancer tissue temperature). Only 20% DOX was released at 37 °C while up to 90% of drugs were leached out within 2 h. In addition, the presence of esterase triggered the rapid release of DOX as well (Kashyap et al. 2016).

Amphiphilic (β-aminoester)-grafted-disulfide methoxy polyethylene glycol copolymer (PAE-*g*-DSMPEG) micelles with pH and redox-sensitive properties were recently reported (Bui et al. 2015). The higher release of DOX from the PAE-*g*-DSMPEG micelles was induced in both acidic condition and presence of DTT (reducing agent). The PAE-*g*-DSMPEG/DOX-micelles formulation was highly potent in killing HepG2 cell even at low concentration (30 μg/ml). Although in vitro uptake of DOX by HepG2 cells demonstrated that free DOX were favored compared to PAE-*g*-DSMPEG/DOX-micelles, the in vivo model of HepG2 tumor-bearing mice revealed that micelles formulation was far more superior to free DOX. More specifically, less tumor cells and higher number of apoptotic cells were observed after treatment with PAE-*g*-DSMPEG/DOX-micelles compared to free

DOX (Bui et al. 2015). Meng and coworkers incorporated pH- and light-responsive features into chitosan-based micelles harboring camptothecin (CPT) (Meng et al. 2013). When this CPT formulation was exposed to MCF-7 cells under UV irradiation, the killing of MCF-7 cells was improved almost twofold compared to without UV exposure (Meng et al. 2013).

Recently, a photochemically triggered cytosolic-drug-release nanoparticle (PHANs) was developed based on conjugation of acetylated backbone to hyaluronic acid (HA)amine-containing polypeptide pH-responsive moiety and a photosensitizer, chlorin e6 (Ce6) followed with formation of self-assembled nanoparticle encapsulating DOX (Lee and Na 2014). Under high laser irradiation (1.2 J/cm^2), the localization of DOX/PHANs into HCT-116 cell nucleus cells was improved drastically from 56.7 to 78.8%, as confirmed by the escape of DOX via endosome-lysomomal membrane disruption. In terms of viability of HCT-116 cells, the number of viable cells decreased from the 74.9 to 42.9% with increase in irradiation exposure from 0.6 to 1.2 J/cm^2. Additionally, treatment of CT-26 bearing mice with DOX/PHANs coupled with laser irradiation also displayed similar efficacy (Lee and Na 2014).

4 Conclusions

This review has summarized some recent trends in the development of polymeric nanoparticles for cancer treatment. Nanoparticle-based drug delivery for cancer treatment has progressed tremendously in the last decade. Nanoparticle-based cancer therapeutics has evolved from its original intention to overcome the toxicity and instability issues of chemotherapeutic drugs toward fingerprinting, personalized nanomedicine. The concept of nano-cancer-target is appealing as multifunctional smart nanoparticles could be designed to exploit the pathological, physiological, and microenvironment of tumors to achieve optimal therapeutic efficacy. Various new and improved nanoparticles have undergone preclinical and clinical investigation (Tables 5 and 6). In this aspect, surface-decorated nanoparticles with biological targeting (i.e., folate, aptamer) has enhanced the affinity toward cancer cells. In addition, prolonged circulation of drug nanoparticle is made possible with the incorporation of long-circulating polymers such as PEG. The ‘stealth-like’ properties of nanoparticles are attractive to reduce drug-associated toxicity. The development of nanoparticle to deliver combination chemotherapeutics is also extensively studied. To further improve the treatment, researchers should explore the use of chemosensitizer and radiosensitizer in conjunction with drugs nanoparticles. Examples include siRNA and curcumin that sensitize the cancer leading to lower drug dosage. Following the success of first generation of nanomedicine, novel nanoparticles with complex stimuli-responsive drug release such as light, temperature, and ultrasound are also under clinical trial investigations. With the current development of nanomedicine, it is entirely plausible that the use of nanoparticle-based cancer therapeutics will be mainstream in the near future.

Table 5 Chemotherapeutics drug delivery with polymeric micelles: marketed and under clinical evaluation

Product name	Type of polymer	Type of drug	Type of cancer targeting	Status	References
Genexol-PM	PEG-poly(D,L-lactide)	PTX	Breast cancer and lung cancer	Marketed	
Genexol-PM	PEG-poly(D,L-lactide)	PTX	Metastatic breast cancer	Phase 3	NCT01644890
NK105	mPEG-poly(aspartic acid)	PTX	Gastric cancer	Phase 2	Kato et al. (2012)
NK105	mPEG-poly(aspartic acid)	PTX	Metastatic breast cancer	Phase 3	NCT01644890
NK105	mPEG-poly(aspartic acid)	PTX	Advanced stomach cancer	Phase 2	Hamaguchi et al. (2007)
NK911	mPEG-poly(aspartic acid)	DOX	Solid tumor	Phase 1	Matsumura et al. (2004)
SP1049C	Pluronic L61 and F127	DOX	Advanced adenocarcinoma of the esophagus and gastroesophageal junction	Phase 2	Valle et al. (2011)
NC-6004	mPEG-poly(glutamic acid)	Cisplatin	Solid tumors	Phase 1	Plummer et al. (2011)
NC-6004	mPEG-poly(glutamic acid)	Combination therapy with NC-6004 and gemcitabine	Locally advanced pancreatic cancer Metastatic pancreatic cancer	Phase 3	NCT02043288
NC-6004	mPEG-poly(glutamic acid)	Combination therapy of NC-6004 (nanoplatin) and gemcitabine	Locally advanced and metastatic pancreatic cancer	Phase 1 and 2	NCT00910741
NK012	mPEG-poly(glutamic acid)	SN38	Lung cancer and triple negative breast cancer	Phase 1 and 2	Matsumura (2011)
NK012	mPEG-poly(glutamic acid)	SN38	Solid tumor	Phase 1	Hamaguchi et al. (2010)

Table 6 Chemotherapeutics drug delivery with polymeric nanoparticles: marketed and under clinical evaluation

Product name	Type of polymer	Type of drug	Type of cancer targeting	Status	References
CRLX101	Cyclodextrin-poly(ethylene glycol) copolymer	CPT	Various cancers	Phase 2	
CT-2103	Polyglutamate	PTX	Persistent ovarian epithelial cancer or primary peritoneal cancer	Phase 2	NCT00045682
CT-2103	Polyglutamate	PTX	Ovarian epithelial or fallopian tube cancer or Primary peritoneal cancer	Phase 2	NCT00017017
CT-2103	Polyglutamate	PTX	Lung cancer	Phase 3	Langer et al. (2008)
CT-2103 (Xyotax)	Polyglutamate	PTX	Breast and metastatic breast cancer	Phase 2	NCT00148707
BIND-014	PLGA/PLA-PEG	DTX	Urothelial carcinoma Cholangiocarcinoma Cervical cancer Squamous cell carcinoma of head and neck	Phase 2	NCT01574274
BIND-014	PLGA/PLA-PEG	DTX	Metastatic castration-resistant prostate cancer	Phase 2	NCT01812746
BIND-014	PLGA/PLA-PEG	DTX	Lung cancer	Phase 2	NCT01792479
Transdrug®	poly(isohexyl cyanoacrylate)	DOX	Advanced hepatocellular carcinoma	Phase 3	NCT01655693
	Polybutylcyanacrylate	Mitoxantrone	Hepatocellular carcinoma	Phase 2	Zhou et al. (2009)

However, there are still limited clinical data to fully understand the implications of nanoparticle-based therapeutics. In addition, the numbers of FDA-approved nanomedicine for clinical use are still very few. One of the contributing factors is the uncertain biosafety issue and nanoparticle-cell interaction in human bodyas well as lack of established clinical protocols for nanomedicine development. Therefore, it is crucial that clinical investigators should fully understand the characteristics of their nanoparticles for a well-designed clinical trial.

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