

# Photo-Responsive Polymeric Nanocarriers for On-Demand Drug Delivery

Jian Ji and Qiao Jin

**Abstract** Polymeric assemblies self-assembled from amphiphilic copolymers are the topic of intense research and have emerged as versatile drug nanocarriers in the past few decades. To enhance the bioavailability of drugs at the target disease site, the use of stimuli-responsive nanocarriers with triggered release properties is highly desired. Among all the available chemical and physical stimuli, photo has attracted much attention since it can be localized in time and space, and it can also be triggered from outside of the system. In this chapter, we highlight the recent progress of photo-responsive assemblies as drug nanocarriers. Different types of photo-responsive polymers were classified. A wide variety of photo-responsive moieties, including UV and NIR responsive polymers, as well as synthetic routes were introduced to the drug nanocarriers. Finally, we suggest possible future developments of photo-responsive polymeric nanocarriers for biomedical applications, especially for drug delivery.

**Keywords** Photo-responsive · Drug delivery · NIR · UV · Micelle · Nanocarrier

## Abbreviations

UV	Ultra violet
NIR	Near-infrared
NIPAAm	N-isopropylacrylamide
OEGMA	Oligo(ethylene glycol) monomethyl ether methacrylate
DOX	Doxorubicin
NBA	O-nitrobenzyl acrylate

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DENBMA	5-(2'-(dimethylamino)ethoxy)-2-nitrobenzyl methacrylate
RAFT	Reversible addition–fragmentation chain transfer polymerization
BSA	Bovine serum albumin
DNQ	2-Diazo-1,2-naphthoquinone

## 1 Introduction

There are a lot of anticancer drugs that have been developed for the treatment of cancers, but their clinical outcomes are always disappointing due to severe side effects. The lack of tumor selectivity and recurrence of cancers with intrinsic or acquired drug resistance will also decrease the therapeutic efficacy of the drugs. Various nanocarriers, including micelles, vesicles, nanoparticles, nanogels, and liposomes have been developed to address these problems (Wei et al. 2013; Sailor and Park 2012; Li et al. 2013). Generally, the drugs can either be physically encapsulated into the hydrophobic inner cores of nanocarriers or chemically conjugated to the polymer chains to form polymer-drug conjugates. Compared to conventional formulation technology, the polymeric nanocarriers have many advantages, including: (1) accumulation passively in solid tumors by enhanced permeation and retention (EPR) effects; (2) avoiding clearance from the reticuloendothelial system; (3) reducing the multiple drug resistance; (4) improving drug pharmacokinetics and biodistribution in vivo (Elsabahy and Wooley 2012; Cabral et al. 2011).

As soon as the drug nanocarriers arrive at the target disease site, a triggered release of encapsulated drugs will be highly desired. As a result, stimuli-responsive nanocarriers, which can show sharp and eventually reversible responses to various environmental changes have found ever-increasing opportunities. Various chemical and physical stimuli, such as pH, redox, temperature, enzyme, have been used to construct stimuli-responsive nanocarriers (Gil and Hudson 2004; Srinivas et al. 2008; Rapoport 2007). This will increase the feasibility of obtaining local high-dose therapy in cancerous tissues and at intracellular compartments. Especially, taking advantage of internal stimuli, such as low pH values of endosome and lysosome (5.0–5.5), lower extracellular pH (6.5) and glutathione (GSH) concentration gradients in tumor tissues, various stimuli-responsive nanocarriers have been designed that can release the endogenous triggered on-demand drug release (Du et al. 2011; Christie et al. 2011). For the above-mentioned endogenous triggered drug release (pH, redox potential, enzyme), it is still a considerable challenge to realize accurately controlled release due to the complex and still not fully understood physiological environment in cells, tissue and body. Thus, it would be favorable to develop a new kind of externally triggered release of drugs in vivo and/or in vitro. Photo is quite advantageous since it can be localized in time and space, and it can also be triggered from outside of the system (Gohy and Zhao 2013; Liu et al. 2013; Habault et al. 2013; Pasparakis et al. 2012; Jin et al. 2010).

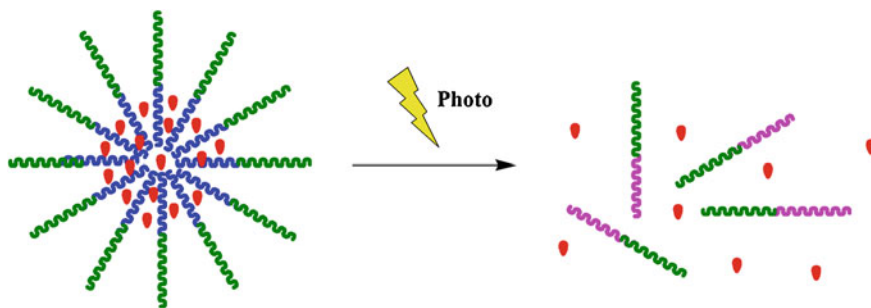
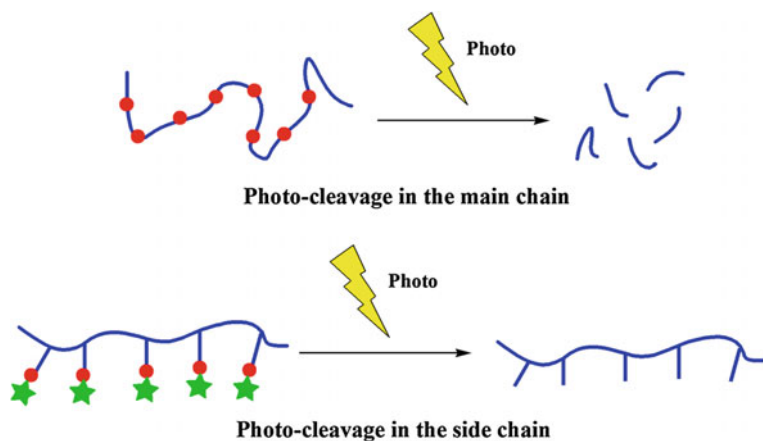


Fig. 1 Photo-responsive drug release from polymeric micelles

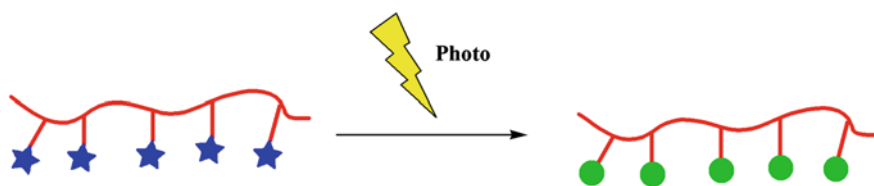
Furthermore, the wavelength and energy of photo can be facile adjusted. The basic design of photo-responsive drug delivery system is shown in Fig. 1. Hence, the advantages of photo-responsive polymeric micelles may include: (1) realizing spatiotemporal drug release with a high local concentration in the diseased sites, and reduce the overall injected dose and systemic toxicity; (2) realizing pulsed drug release; (3) controlling the targeting properties of nanocarriers.

## 2 Classify of Photo-Responsive Polymers

With the development and applications of photo-responsive materials in diverse fields including catalysis, sensors, templates, etc., various photo-responsive polymers have been designed. Depending on different premises, photo-responsive polymers can be classified in different ways. Based on the reversibility, photo-responsive polymers can be classified as reversible and irreversible photo-responsive polymers. Meanwhile, they can also be classified into UV, visible light and NIR responsive polymers depending on the light source. Additionally, based on the reaction mechanisms, photo-responsive polymers can be classified as photo-cleavable polymers and photo-isomerized polymers. In the presence of photo irradiation, photo-cleavable polymers will be degraded or the side group of the polymers will be cleaved (Fig. 2). On the contrary, photo-isomerized polymer will be isomerized to another polymer under photo irradiation (Fig. 3). Table 1 summarizes different types of photo-responsive groups, which might be helpful for the rational design of photo-responsive polymers in biomedical applications. The self-assembly and intracellular on-demand drug delivery of photo-responsive polymers will be discussed in detail in this chapter.



**Fig. 2** Schematic illustration of photo-cleavage reaction



**Fig. 3** Schematic illustration of photo-isomerization reaction

### 3 UV Responsive Polymeric Nanocarriers for Drug Delivery

UV light is widely used for the construction of photo-responsive materials since UV light apparatus with various wavelengths and intensity is cheap and easily set up in laboratory. What's more, most of the photo-responsive groups are UV light sensitive. In general, low-power photo irradiation of long wavelength UV light (365 nm) within 30 min is safe to body and imposes little toxicity to cells. However, it is enough for most of the photo reactions and photo-responsive drug release can be achieved, which opens a door for the design of UV responsive nanocarriers. Since photo-responsive pyrene-containing amphiphilic diblock copolymers were first introduced as drug delivery vehicles in 2005 by Yue Zhao (Jiang et al. 2005), there has been considerable interest in photo-responsive polymeric micelles for on-demand drug-delivery.

**Table 1** Characteristic features of photo-responsive groups

Photo-responsive group	Light source	Reversibility	Effect of photo	Polymer design
O-nitrobenzyl ester	UV, NIR	No	Photocleavage	Side-chain (Jiang et al. 2006), main-chain (Han et al. 2011)
Azobenzene	UV	Yes	Photoisomerization	Side-chain (Jin et al. 2010)
Spiropyran	UV	Yes	Photoisomerization	Side-chain (Jin et al. 2010)
Coumarinyl ester	UV, NIR	No	Photocleavage	Side-chain (Babin et al. 2009)
2-diazo-1,2-naphthoquinone	UV, NIR	No	Photocleavage	Side-chain (Chen et al. 2011)
Pyrenylmethyl ester	UV	No	Photocleavage	Side-chain (Jiang et al. 2005)

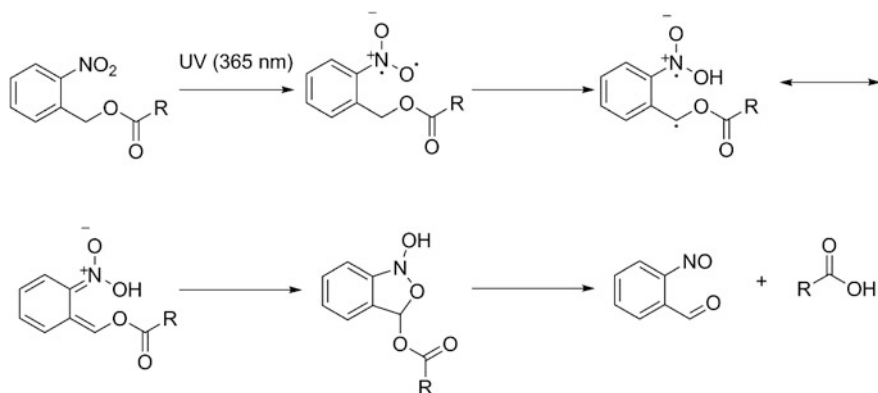
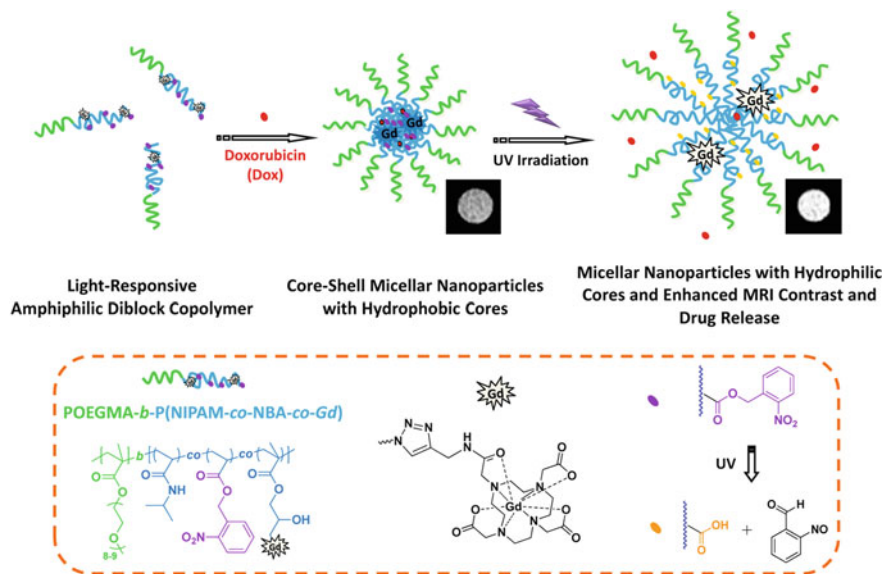


Fig. 4 The mechanism of photocleavage of *o*-nitrobenzyl ester

### 3.1 *O*-Nitrobenzyl Containing Drug Nanocarriers

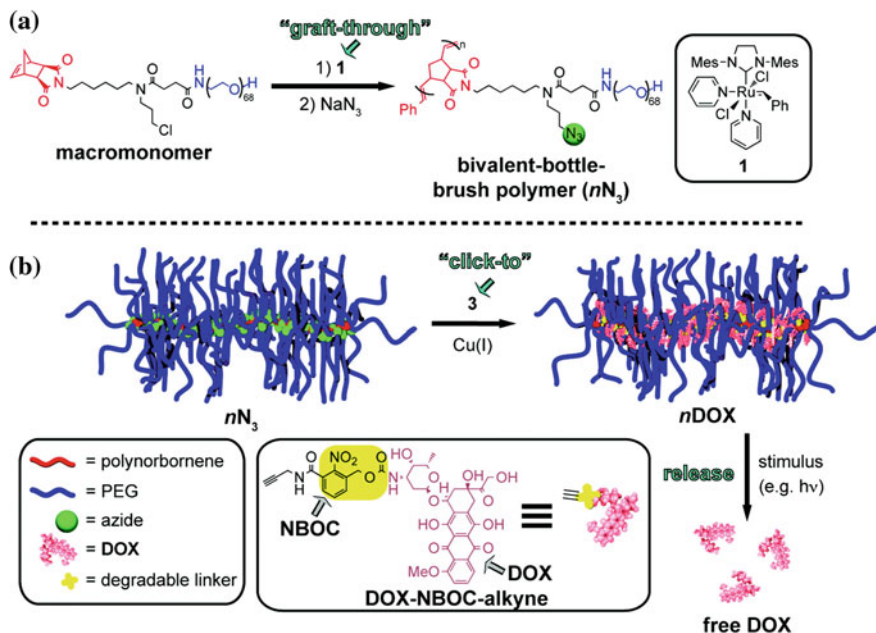
As a most widely studied photo-labile group, the *o*-nitrobenzyl group is utilized frequently in polymer and materials science. *o*-Nitrobenzyl ester has become one of the most popular photo-labile protecting groups since first described by Schofield and co-workers (Bartrop et al. 1966). The photocleavage of *o*-nitrobenzyl ester is an intramolecular rearrangement process and the mechanism of the photocleavage of *o*-nitrobenzyl ester to corresponding *o*-nitrosobenzaldehyde upon UV irradiation is shown in Fig. 4. It is very important that this kind of photo-reaction doesn't need protonic solvent and can carry out both in solution and solid state. Moreover, the photocleavage of *o*-nitrobenzyl can occur via one-photon UV (365 nm) or two-photon (700 nm) irradiation. The photo-cleavable *o*-nitrobenzyl group can be conjugated either in the side chain or in the main chain. If it is in the side chain, the hydrophobic *o*-nitrobenzyl containing block will transform to hydrophilic carboxylic acid containing block under UV irradiation, which will result in the hydrophobicity-to-hydrophilicity transition. If *o*-nitrobenzyl group is in the main chain, the polymer backbone will be degraded into small molecules under UV irradiation.

The first example of photo-responsive *o*-nitrobenzyl containing micelles was reported by Zhao and co-workers (Jiang et al. 2006). They synthesized amphiphilic block copolymer poly(ethylene oxide)-*b*-poly(2-nitrobenzyl methacrylate) (PEO-*b*-PNBMA) which can self-assemble into micelles. The photolysis of 2-nitrobenzyl groups resulted in the cleavage of 2-nitrosobenzaldehyde from the polymer, which transformed the hydrophobic PNBMA into the hydrophilic PMAA and triggered the micellar disruption. Using Nile red as a hydrophobic model compound, they investigated the photo-controlled release of Nile red from PEO-*b*-PNBMA micelles. The release of Nile red was monitored by fluorescence spectra as the fluorescence intensity decreased and the maximum emission wavelength red shifted upon UV irradiation.



**Fig. 5** Schematic illustration for the fabrication of photo-responsive polymeric micelles of POEGMA-*b*-P(NIPAAm-co-NBA-co-Gd) amphiphilic diblock *o*-nitrobenzyl containing copolymer (Li et al. 2012). Reproduced by permission of the American Chemical Society

Similarly, Liu and co-workers fabricated amphiphilic *o*-nitrobenzyl containing diblock copolymer micelles exhibiting photo-triggered hydrophobic-hydrophilic transition within micellar cores and the concomitant enhancement of magnetic resonance (MR) imaging contrast performance and release rate of physically encapsulated hydrophobic drugs (Li et al. 2012). POEGMA-*b*-P(NIPAAm-co-NBA-co-Gd) diblock copolymers covalently labeled with Gd<sup>3+</sup> complex were synthesized via the combination of consecutive RAFT polymerizations and “click” postfunctionalization. Self-assembled micelles were further used to encapsulate anticancer drug DOX. In the presence of UV irradiation, hydrophobic NBA moieties transformed into hydrophilic carboxyl derivatives, resulting in the changes of micellar microstructural changes and the core swelling. As a result, the microenvironment surrounding Gd<sup>3+</sup> complexes was subjected to a transition from being hydrophobic to hydrophilic, which led to the enhancement of MR imaging contrast performance. At the same time, the release rate of encapsulated Dox was also enhanced (Fig. 5). In another research, the same group fabricated photo-degradable, protein-polyelectrolyte complex-coated, mesoporous silica nanoparticles (MSNs) and realized controlled co-release of protein and model drugs (Wan et al. 2013). Random copolymers composed of OEGMA and a photocleavable *o*-nitrobenzyl-containing monomer, DENBMA, were first conjugated to MSNs by RAFT and then quaternary aminated to obtain positively charged P(OEGMA-co-TENBMA) which exhibits photo-induced charge conversion characteristics. Rhodamine B (RhB) was encapsulated into the nanopores of



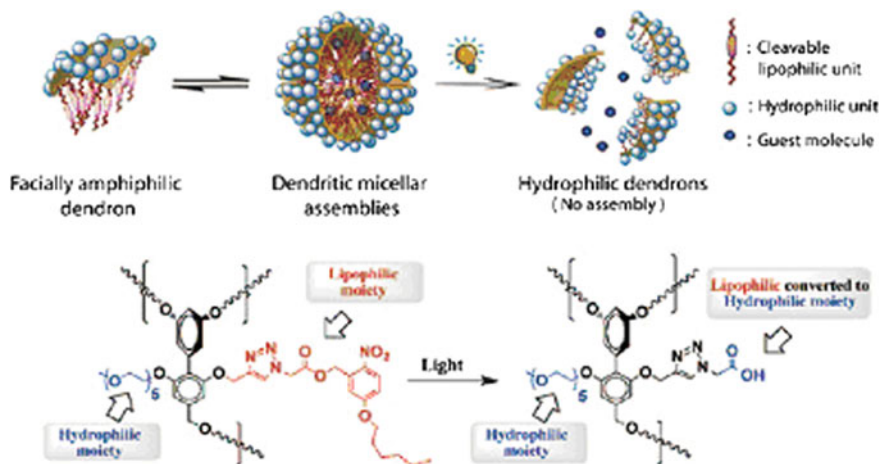
**Fig. 6** a Synthesis of the polymer-drug conjugates; b Photo-triggered release of DPOX from the polymer-drug conjugates (Johnson et al. 2011). Reproduced by permission of the American Chemical Society

the MSNs. Meanwhile, Negatively charged BSA was loaded on the surface of the hybrid MSNs by electrostatic interactions. Upon UV irradiation, positively charged P(OEGMA-co-TENBMA) were transformed to negatively charged, which led to the disruption of protein-polyelectrolyte complex on MSNs and co-release of BSA and RhB by electrostatic repulsion.

In another interesting research, Grubbs and co-workers synthesized photo-responsive o-nitrobenzyl containing polymer-drug conjugates (Johnson et al. 2011). A class of DOX conjugated bottle-brush copolymer nanoconjugates were prepared by ring-opening metathesis polymerization and click chemistry. DOX was conjugated to the backbone by photocleavable o-nitrobenzyl groups (Fig. 6). After UV irradiation, DOX was cleaved from the backbone and the free DOX could kill the cancer cells effectively.

Besides photo-responsive linear polymers, dendritic amphiphilic o-nitrobenzyl containing Nanocontainers were also reported by Yesilyurt et al. (2011). They designed and synthesized photo-responsive amphiphilic dendrimers that can form dendritic micelles in water. Hydrophobic guest molecules were loaded into the dendritic micelles. Upon UV irradiation, Hydrophobic o-nitrobenzyl ester groups were converted to hydrophilic carboxylic acid segments, which destroyed the hydrophilic-hydrophobic balance and resulted in the supramolecular disassembly of the dendritic micelles (Fig. 7). 88 % of the encapsulated guest molecules were



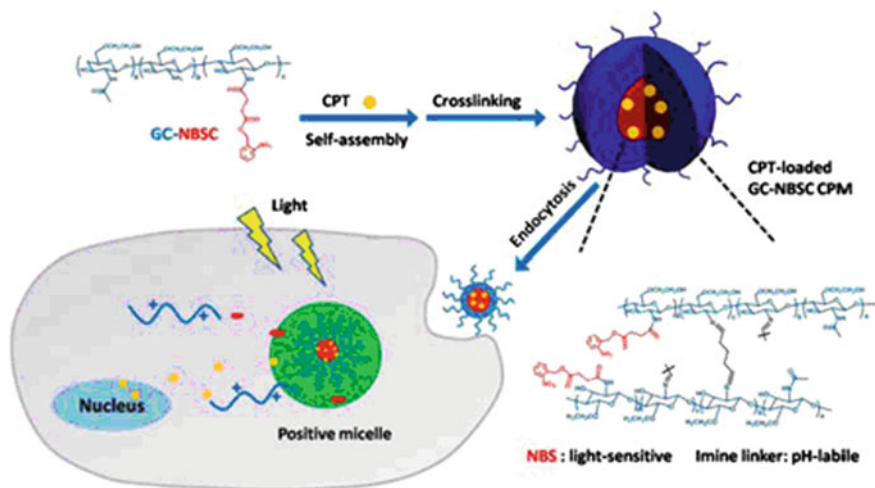


**Fig. 7** Photo-induced disassembly of dendritic micellar assemblies after photo irradiation (Yesilyurt et al. 2011). Reproduced by permission of John Wiley and Sons

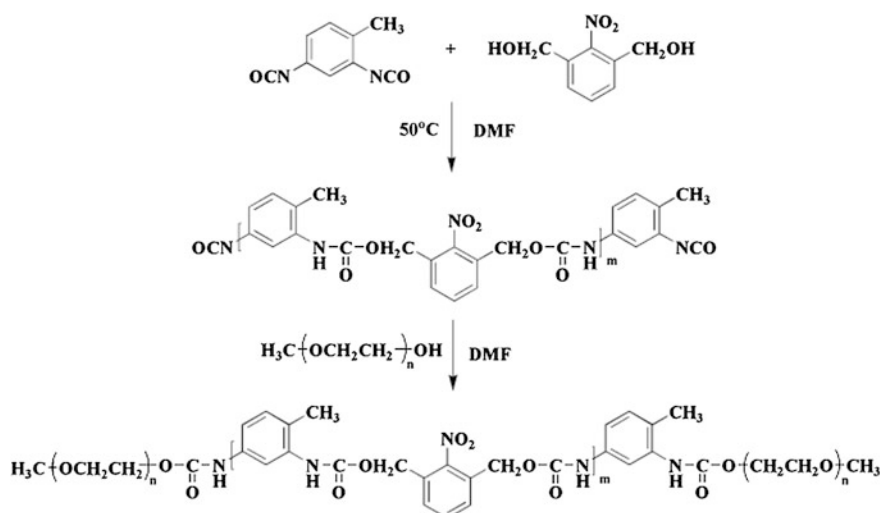
released in only 200s upon UV irradiation, compared to the 5 % guest release upon irradiation of a control dendrimer, which lacked the photolabile *o*-nitrobenzyl groups.

Combining photo with other stimuli can significantly broaden the scope of applications of such drug nanocarriers. Very recently, Zhu and co-workers reported chitosan-based nanocarriers with pH and photo dual response for anti-cancer drug delivery (Meng et al. 2013). The pH and photo-responsive cross-linked polymeric micelles were prepared by the self-assembly of amphiphilic glycol chitosan-*o*-nitrobenzyl succinate conjugates and then cross-linking with glutaraldehyde, which was synthesized by grafting photo-responsive *o*-nitrobenzyl group onto hydrophilic glycol chitosan. Anticancer drug camptothecin (CPT) can be loaded into the micelles. The *in vitro* drug release experiments showed the encapsulated CPT could be quickly released at low pH with UV irradiation (Fig. 8). At the same time, the CPT-loaded micelles exhibited better cytotoxicity against cancer cells under UV irradiation.

The *o*-nitrobenzyl groups mentioned above are all in the side chains. Zhao and co-workers also conjugated *o*-nitrobenzyl groups in the main chains. In one their research (Han et al. 2011), they synthesized an amphiphilic ABA triblock copolymer PEO-*b*-PUNB-*b*-PEO of which the middle block PUNB is a hydrophobic polyurethane containing *o*-nitrobenzyl groups (Fig. 9). The resulting micelles possess a photodegradable core and can be disrupted very fast upon UV irradiation. As a result, more than 70 % of encapsulated guest molecules can be released after only 10 s of UV irradiation (365 nm). What's more, they prepared block copolymer micelles with a dual-stimuli degradable core for fast or slow drug release (Han et al. 2012). ABA triblock copolymer PEO-*b*-poly(disulfide-*alt*-nitrobenzene)-*b*-PEO was synthesized by two-step click chemistry of which the

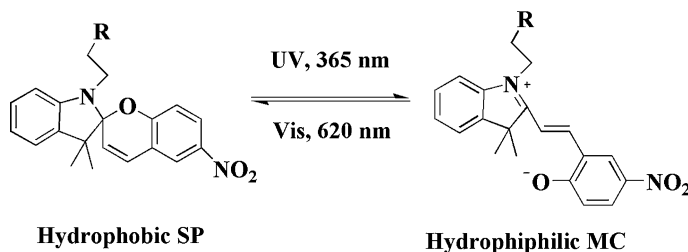


**Fig. 8** Schematic illustration for the preparation of CPT-loaded micelles and intracellular drug release triggered by pH and UV Light (Meng et al. 2013). Reproduced by permission of the American Chemical Society



**Fig. 9** Synthesis of photo-degradable triblock copolymer of PEO-b-PUNB-b-PEO (Han et al. 2011). Reproduced by permission of the American Chemical Society

middle block is composed of redox-responsive disulfide and photo-responsive *o*-nitrobenzyl groups. With this design, the micelles be disrupted under the effect of either a reducing agent DTT that breaks the disulfide bonds or UV light that cuts the *o*-nitrobenzyl ester groups. This feature makes it possible to have either burst



**Fig. 10** Photo-responsive reversible spiroopyran-merocyanine (SP-MC) transition

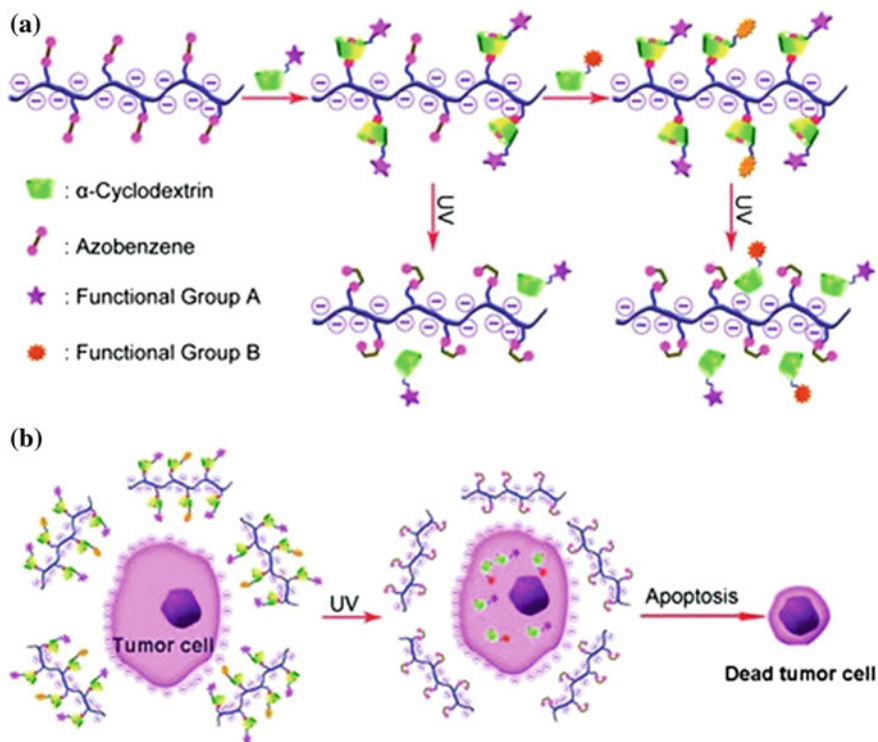
release of encapsulated guest molecules by UV irradiation, or slow release by the action of a reducing agent DTT in the micellar solution. The two stimuli could also be utilized in combination to generate on-demand release rate profiles.

### 3.2 Spiropyran-Containing Drug Nanocarriers

Photochromic spiroopyran molecules are well known for the reversible spiroopyran-merocyanine (SP-MC) transition (Goldburt et al. 1984). The SP molecule is colorless, nonpolar, hydrophobic, and in a “closed” form under visible light irradiation (620 nm). Exposure of the SP molecule to UV (365 nm) irradiation induces ring-opening isomerization, giving the colored, polar, hydrophilic, and zwitterionic MC form (Fig. 10). Recently, the spiroopyran-merocyanine (SP-MC) chemistry has been introduced to construct photo-responsive nanocarriers. Lee and co-workers synthesized a diblock copolymer PEO-*b*-PSPMA, where SPMA was spiroopyran-containing methacrylate monomer (Lee et al. 2007). The SP units respond to photo and undergo a reversible isomerization between hydrophobic SP and hydrophilic MC, which results in the assembly and disassembly of the micelles. This micelle system was successfully applied to the efficient encapsulation, release, and partial re-encapsulation of hydrophobic guest molecules. Similarly, Ji and co-workers synthesized amphiphilic spiroopyran-containing hyperbranched polyphosphate HPHEEP-SP which can self-assemble to biocompatible micelles (Chen et al. 2012). Model drug coumarin 102 was then encapsulated into the micelles successfully. Photo-controlled release and re-encapsulation was also realized.

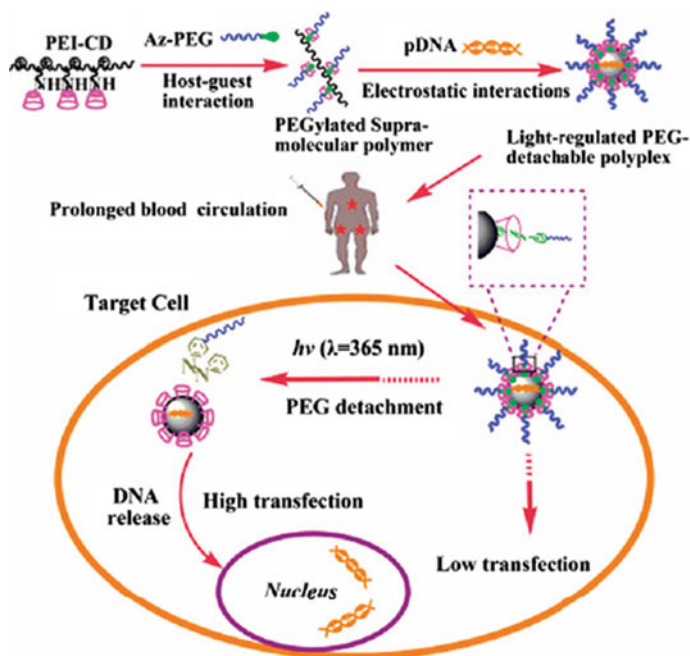
### 3.3 Azobenzene-Containing Drug Nanocarriers

Azobenzene can undergo trans-cis photoisomerization in response to UV and visible light which results in large structural change as reflected in the spatial requirement and absorption spectra (Tamai and Miyasaka 2000). At the same time, trans-azobenzene is an excellent guest for inclusion complexation with  $\alpha$ - and



**Fig. 11** Schematic illustration of the photo responsive polyanionic template loading (a) and release (b) of  $\alpha$ -CD modified drug and functional groups (Xiao et al. 2011). Reproduced by permission of John Wiley and Sons

$\beta$ -cyclodextrin (CD). In contrast, *cis*-azobenzene cannot form inclusion complexation with CD because of the mismatch between the host and the guest. This photo-switchable host-guest interaction might be a nice inspiration for the design of smart drug nanocarriers (Wang et al. 2007). Zhang and co-workers fabricated cellular-uptake shielding “Plug and Play” template for photo triggered drug release (Xiao et al. 2011). The polyanionic template consisted of polyacrylic acid (PAA) and azobenzene. The  $\alpha$ -CD modified drug or functional groups can be loaded onto the template via host-guest interaction. Upon UV irradiation, the  $\alpha$ -CD modified drug can be released (Fig. 11). Since the surface of cells is negatively charged, the negatively charged drug carriers will be repelled by cells and cannot be uptaken by normal cells. In the presence of UV irradiation, the loaded drug can be released from the drug carrier quickly and thereafter endocytosed by target cells to achieve the desirable cure effect. Azobenzene-containing photo-responsive amphiphilic linear-dendritic block copolymers were reported by Oriol and co-workers recently (Blasco et al. 2013). The release of encapsulated guest molecules can be triggered by low intensity UV illumination, which was related to the *trans-cis* photoisomerization of azobenzene.

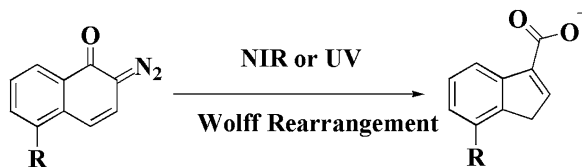


**Fig. 12** Formation of PEGylated polyplexes via host–guest interactions and the detachment of PEG upon UV irradiation (Li et al. 2012). Reproduced by permission of the Royal Society of Chemistry

Photo-responsive azobenzene-containing polymers can also be used in gene delivery. Wang and co-workers constructed intracellular PEG-detachable polyplexes to facilitate nuclear entry by photo-responsive host–guest interactions (Li et al. 2012). They synthesized  $\beta$ -CD-modified branched polyethylenimine (PEI-CD) and azobenzene modified PEG (AZ-PEG) was grafted to PEI-CD via host–guest interactions. By this way, PEGylated supramolecular PEI (Az-PEG/PEI-CD) was prepared. It was used to associate with DNA and Az-PEG/PEI-CD/DNA polyplexes were obtained. PEGylated polyplexes provided excellent biocompatibility during circulation. After they were internalized by cells, photo-regulated dePEGylation facilitated DNA release and nuclear entry, thus resulting in efficient transfection (Fig. 12).

#### 4 NIR Responsive Polymeric Nanocarriers for Drug Delivery

As is known, UV light can be easily absorbed by water and biomolecules. As a result, UV light can only penetrate shallow tissue, which greatly limits the applications of UV light in vivo. What's more, UV light is somewhat harmful

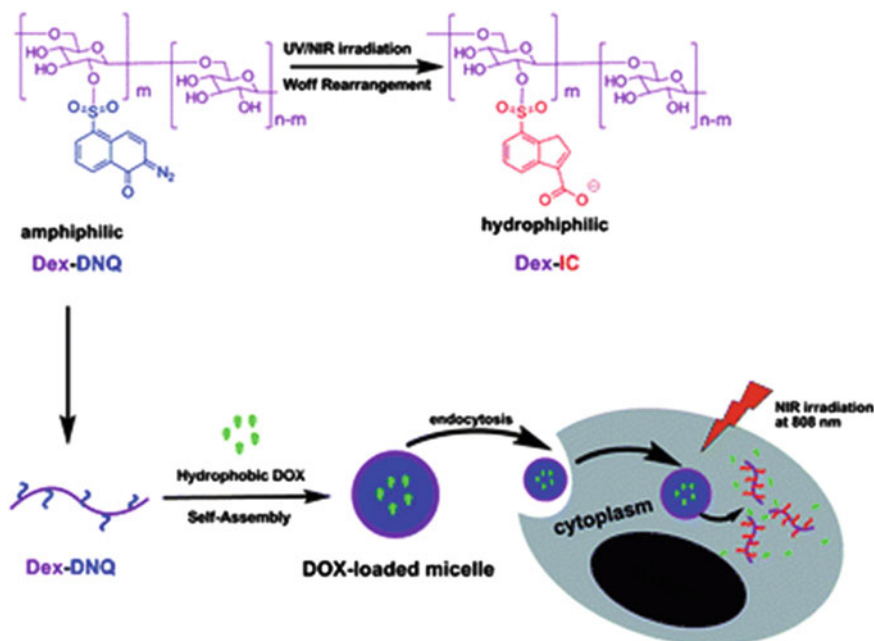


**Fig. 13** Wolff rearrangement of DNQ

to the tissues and cells. To overcome this drawback, an increasing number of drug-delivery materials sensitive to near infrared (NIR) light have been reported in recent years. Compared to UV light, NIR between 700 and 1,000 nm can penetrate several millimeters up to centimeter depth of tissues and shows fewer risks of damage to the irradiated area, enabling the NIR-sensitive nanomedicines great potential as a noninvasive clinical therapy (Fomina et al. 2012; Weissleder 2001).

#### 4.1 DNQ-Containing Drug Nanocarriers

2-Diazo-1,2-naphthoquinone (DNQ) is one of the most widely used NIR responsive groups in scientific research. Under UV (365 nm) or NIR (800 nm) irradiation, the hydrophobic DNQ undergoes a Wolff rearrangement to afford hydrophilic 3-indenecarboxylic acid with a pKa of 4.5 (Fig. 13) (Almstead et al. 1994). Therefore, the DNQ-containing polymers provide a versatile platform for the design of NIR-responsive drug nanocarriers. Fréchet and co-workers first synthesized amphiphilic copolymers of DNQ-terminated PEO (PEO-DNQ) (Goodwin et al. 2005). PEO-DNQ can self-assemble into micelles for the encapsulation of hydrophobic Nile Red. The photo-responsive release of Nile Red was monitored by fluorescence spectra under NIR irradiation (795 nm). The disadvantage of this system was that PEO-DNQ had a relatively high critical micelle concentration (CMC) of 0.15 mg/mL and exhibited a rather high toxicity towards cells. In order to overcome this disadvantage, they synthesized DNQ-containing linear-dendritic copolymers, which showed much lower CMC (12  $\mu$ g/mL) and was less toxic than PEO-DNQ. Meanwhile, the NIR-responsive release of guest molecules was also realized (Mynar et al. 2007). Notably, Ji and co-workers designed a series of DNQ modified polymers, including hyperbranched polyphosphate, comb-like PEG, and dextran to explore the NIR-responsive drug release (Chen et al. 2011a, b; Liu et al. 2012). Especially, they constructed DNQ grafted dextran (Dex-DNQ), which was used for the NIR-responsive intracellular drug delivery (Liu et al. 2012). Anti-cancer drug DOX can be easily encapsulated into Dex-DNQ micelles with loading content of 24 %. In vitro cell viability studies, the micelles exhibited higher intracellular DOX release under NIR irradiation at 808 nm, which resulted in significant growth inhibition of HepG2 cancer cells (Fig. 14).

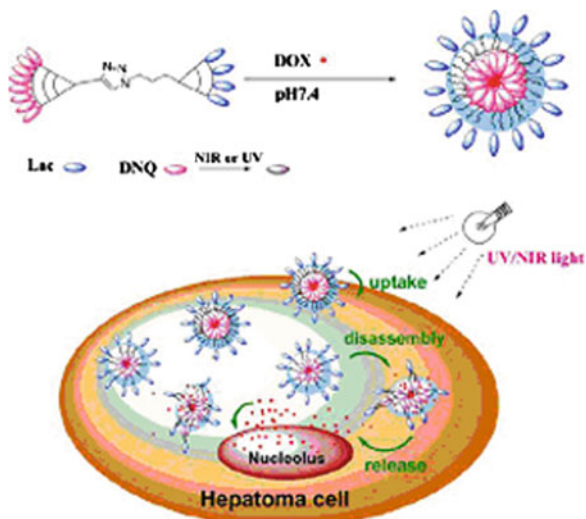


**Fig. 14** Schematic illustration of the self-assembly and NIR-responsive intracellular release of DOX (Liu et al. 2012). Reproduced by permission of the Royal Society of Chemistry

Importantly, DNQ was introduced into multifunctional drug nanocarriers. Dong and co-workers prepared NIR-responsive sugar-targeted nanocarriers from degradable and dendritic amphiphiles (Sun et al. 2011). They synthesized DNQ grafted dendritic poly(amido amine)-b-poly( $\epsilon$ -caprolactone) (D3-PCL-DNQ), D3-PCL-DNQ micelles can be used as nanocarriers for the loading of DOX. Upon NIR irradiation, DOX can be released in a controlled manner by changing the photo irradiation time, which was induced by the gradual disruption of micelles in aqueous solution. Furthermore, the sugar-coated micelles demonstrated specific binding with the lectins Concanavalin A and Ricinus communis agglutinin, respectively, which made them useful as targeted drug-delivery vesicles. In another research, the same group fabricated NIR-responsive and lectin-binding nanocarriers from Janus-type dendritic PAMAM amphiphiles (Sun et al. 2012). Janus-type dendritic poly(amido amine) (PAMAM) amphiphiles Dm-Lac-D3DNQ were synthesized by connecting hydrophobic DNQ-decorated PAMAM dendron D3 and hydrophilic lactose (Lac)-decorated PAMAM dendrons Dm via click chemistry. Amphiphilic Dm-Lac-D3DNQ can self-assemble into the DNQ-cored micelles dangled by densely free Lac groups (Fig. 15). After 30 min of NIR irradiation (808 nm), most of the micelles were disassembled. The DOX-loaded nanomedicine exhibited a NIR-triggered drug release profile and a related cytotoxicity that was close to free DOX. Meanwhile, the micelles showed binding with RCA<sub>120</sub> lectin, which was related to the generation of Lac-decorated dendrons.

**Fig. 15** Self-assembly of DOX-loaded nanocarriers of Dm-Lac-D3DNQ and NIR-responsive intracellular DOX release (Sun et al. 2012).

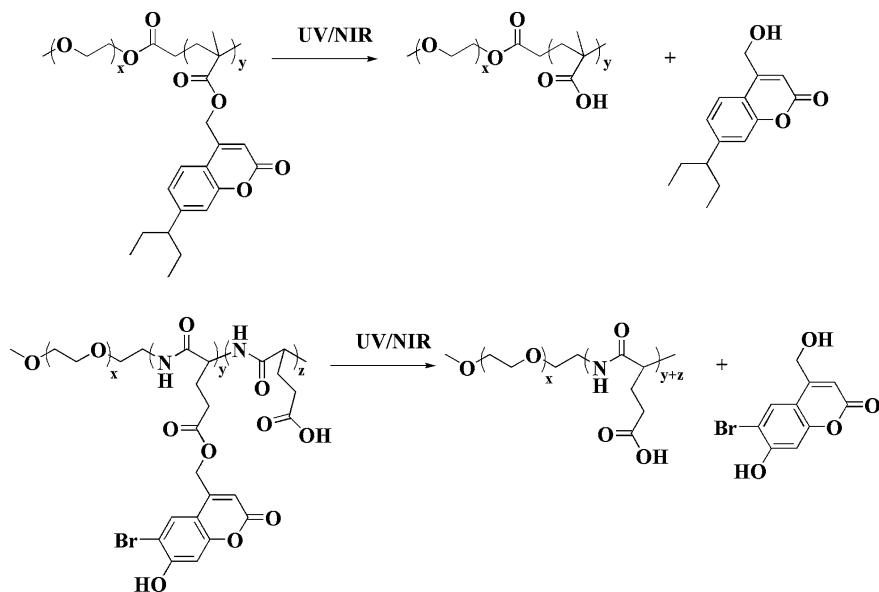
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## 4.2 Coumarin-Containing Drug Nanocarriers

The coumarin family has thousands of derivatives and has been widely used in various areas. The coumarin units are well known for the reversible dimerization and de-dimerization under UV irradiation with different wavelength (365 and 254 nm) (Trenor et al. 2004). Thus, coumarin units are widely used in photo cross-linking. On the other hand, some special coumarin derivatives can also be photocleaved under one-photon UV or two-photon NIR irradiation if the coumarin derivatives are linked along the side chain of polymer by ester units (Fig. 16). Zhao and co-workers first synthesized coumarin-containing NIR-responsive nanocarriers. The amphiphilic NIR-responsive block copolymer is composed of hydrophilic PEO block and hydrophobic poly-([7-(diethylamino)coumarin-4-yl] methyl methacrylate) (PDEACMM) block (Babin et al. 2009). Upon UV or NIR irradiation, the DEACMM groups were cleaved from the backbone, which converted the ester groups to carboxylic acid groups and the hydrophobic PDEACMM to hydrophilic poly(methacrylic acid) (PMA). After 285 min of NIR exposure, micelles appeared to be highly degraded, accompanying with the release of guest molecules. In order to improve the biocompatibility and biodegradability of the micelles, Zhao and co-workers a new kind of polypeptide copolymer (Kumar et al. 2012). The NIR responsive copolymer was composed of PEO and poly(L-glutamic acid) bearing a number of 6-bromo-7-hydroxycoumarin-4-ylmethyl groups (PEO-b-P(LGA-co-COU)). The coumarin compound, 6-bromo-7-hydroxycoumarin-4-ylmethyl, was selected as the NIR-responsive group because this chromophore is known to have a large two-photon absorption cross-section for NIR light. The PEO-b-P(LGA-co-COU) micelles could be disrupted by 794 nm NIR excitation via two-photon absorption. The NIR-responsive release of an antibacterial drug



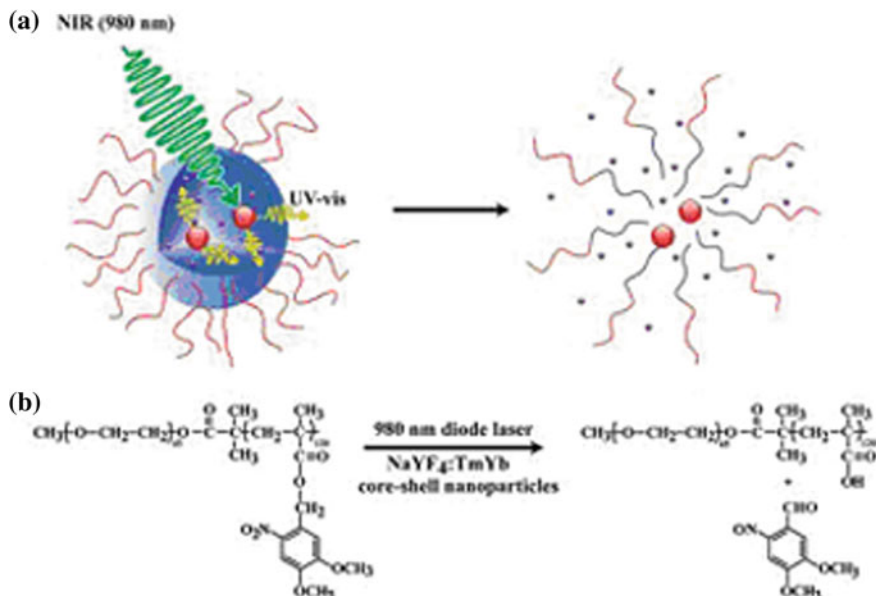


**Fig. 16** NIR responsive coumarin derivatives PEO-b-PDEACMM and PEO-b-P(LGA-co-COU) (Babin et al. 2009; Kumar et al. 2012)

(Rifampicin) and an anticancer drug (Paclitaxel) loaded into the PEO-b-P(LGA-co-COU) micelles was further investigated. They found that the two drugs could be released effectively upon NIR light exposure of the micellar solution.

### 4.3 Upconverting Nanoparticles-Assistant NIR Responsive Drug Nanocarriers

As mentioned above, most of the NIR-responsive nanocarriers are triggered by two-photon absorption of NIR light. However, the photoreactions activated by two-photon absorption of NIR light are generally slow and inefficient due to the low two-photon absorption cross sections of the chromophores. Moreover, the simultaneous absorption of two photons necessitates high laser power density and therefore requires a femtosecond pulse laser. Recently, upconverting nanoparticles (UCNPs) have emerged as an appealing candidate for the application of NIR light (Yang et al. 2012; Gu et al. 2013). Because of the unique ladder-like energy level structures of lanthanide ions (such as  $\text{Tm}^{3+}$ ,  $\text{Er}^{3+}$ , and  $\text{Ho}^{3+}$ ), UCNPs are able to absorb NIR light and convert it into high-energy photons in a very broad range from the UV to the NIR region. In contrast to two-photon absorption, the excitation of UCNPs by NIR light occurs via sequential, multiple absorptions with real energy levels, which requires much lower power density so that a continuous-wave



**Fig. 17** **a** Schematic illustration of using NIR light excitation of UCNPs to trigger dissociation of micelles. **b** NIR light-triggered photoreaction with the used micelles of PEO-b-PNBMA and UCNPs (Yan et al. 2011). Reproduced by permission of the American Chemical Society

diode NIR laser can be sufficient as the excitation source. Using UCNPs, some UV responsive systems can be converted to NIR responsive systems. Liu and co-workers prepared silica coated UCNPs and then functionalized with a positively charged alkyl amine by photo-responsive *o*-nitrobenzyl linkers through covalent bonding (Yang et al. 2013). The positively charged nanoparticles can effectively adsorb anionic siRNA through electrostatic attractions and were easily internalized by living cells. Upon NIR light irradiation (980 nm), UCNPs can absorb NIR light and converted it into 365 nm UV light. UV light of 365 nm can cleave the *o*-nitrobenzyl linkers and converted the positively charged alkyl amine to negatively charged carboxyl group. By this way, the intracellular release of the siRNA can be realized. Zhao and co-workers physically encapsulated UCNPs and Nile Red inside micelles of *o*-nitrobenzyl containing poly(ethylene oxide)-block-poly(4,5-dimethoxy-2-nitrobenzyl methacrylate) (PEO-b-PNBMA) (Yan et al. 2011). When exposing the micellar solution to 980 nm NIR light, photons in the UV region (365 nm) were emitted by the UCNPs, which in turn were absorbed by *o*-nitrobenzyl groups on the micelle core-forming block and activated the photocleavage reaction. Finally, the micelles were dissociated and the co-loaded Nile Red was released (Fig. 17). This strategy of using UCNPs as an internal UV or visible light source upon NIR light excitation represents a general and efficient way to circumvent the need of UV or visible light excitation that is a common drawback for photo-responsive systems in biomedical applications.

## 5 Conclusion and Outlook

In this chapter, we highlighted the recent progresses on photo-responsive polymeric nanocarriers that might realize spatiotemporal and on-demand drug delivery via photo irradiation. A wide variety of photo-responsive moieties as well as synthetic routes were introduced to the drug nanocarriers. The nanocarriers exhibited photo responsiveness and showed great potential in clinical medicine and oncology. Despite these advantages, there are still many challenges and issues that need to be addressed. The main limitations include: (1) The NIR-responsive groups are limited. We should discover more NIR responsive groups with a large absorption cross-section ( $>1\text{GM}$ ); (2) The biodegradability and biocompatibility of the drug nanocarriers should be paid great attention to; (3) The cytotoxicity of the by-products resulting from the photo-induced reactions should be concerned. There is still much room in the field of photo-responsive nanocarriers for further development and the development and applications of photo-responsive polymeric nanocarriers will continue in the future.

## References

- Almstead J, Urwyler B, Wirz J (1994) Flash photolysis of alpha-diazonaphthoquinones in aqueous solution: determination of rates and equilibria for keto-enol tautomerization of 1-indene-3-carboxylic acid. *J Am Chem Soc* 116:954–960
- Babin J, Pelletier M, Lepage M et al (2009) A new two-photon-sensitive block copolymer nanocarrier. *Angew Chem Int Ed* 48:3329–3332
- Bartrop JA, Plant PJ, Schofield P (1966) Photosensitive protective groups. *Chem Commun (London)* 22:822–823
- Blasco E, Barrio J, Somolinos C et al (2013) Light induced molecular release from vesicles based on amphiphilic linear-dendritic block copolymers. *Polym Chem* 4:2246–2254
- Cabral H, Nishiyama N, Kataoka K (2011) Supramolecular nanodevices: from design validation to theranostic nanomedicine. *Acc Chem Res* 44:999–1008
- Chen CJ, Liu GY, Shi YT et al (2011a) Biocompatible micelles based on comb-like peg derivatives: formation, characterization, and photo-responsiveness. *Macromol Rapid Commun* 32:1077–1081
- Chen CJ, Liu GY, Liu XS et al (2011b) Photo-responsive, biocompatible polymeric micelles self-assembled from hyperbranched polyphosphate-based polymers. *Polym Chem* 2:1389–1397
- Chen CJ, Jin Q, Liu GY et al (2012) Reversibly light-responsive micelles constructed via a simple modification of hyperbranched polymers with chromophores. *Polymer* 53:3695–3703
- Christie RJ, Miyata K, Matsumoto Y (2011) Effect of polymer structure on micelles formed between siRNA and cationic block copolymer comprising thiols and amidines. *Biomacromolecules* 12:3174–3185
- Du JZ, Du XJ, Mao CQ et al (2011) Tailor-made dual pH-sensitive polymer-doxorubicin nanoparticles for efficient anticancer drug delivery. *J Am Chem Soc* 133:17560–17563
- Elsabagy M, Wooley KL (2012) Design of polymeric nanoparticles for biomedical delivery applications. *Chem Soc Rev* 41:2545–2561
- Fomina N, Sankaranarayanan J, Almutairi A (2012) Photochemical mechanisms of light-triggered release from nanocarriers. *Adv Drug Delivery Rev* 64:1005–1020

- Gil ES, Hudson SM (2004) Stimuli-responsive polymers and their bioconjugates. *Prog Polym Sci* 29:1173–1222
- Gohy J, Zhao Y (2013) Photo-responsive block copolymer micelles: design and behavior. *Chem Soc Rev* 42:7117–7129
- Goldburgt E, Shvartsman F, Fishman S (1984) Intramolecular interactions in photochromic spiropyran-merocyanine polymers. *Macromolecules* 17:1225–1230
- Goodwin AP, Mynar JL, Ma YZ et al (2005) Synthetic micelle sensitive to ir light via a two-photon process. *J Am Chem Soc* 127:9952–9953
- Gu ZJ, Yan L, Tian G et al (2013) Recent advances in design and fabrication of upconversion nanoparticles and their safe theranostic applications. *Adv Mater* 25:3758–3779
- Habault D, Zhang HJ, Zhao Y (2013) Light-triggered self-healing and shape-memory polymers. *Chem Soc Rev* 42:7244–7256
- Han DH, Tong X, Zhao Y (2011) Fast photodegradable block copolymer micelles for burst release. *Macromolecules* 44:437–439
- Han D, Tong X, Zhao Y (2012) Block copolymer micelles with a dual-stimuli-responsive core for fast or slow degradation. *Langmuir* 28:2327–2331
- Jiang J, Tong X, Zhao Y (2005) A new design for light-breakable polymer micelles. *J Am Chem Soc* 127:8290–8291
- Jiang J, Tong X, Morris D et al (2006) Toward photocontrolled release using light-dissociable block copolymer micelles. *Macromolecules* 39:4633–4640
- Jin Q, Liu GY, Ji J (2010a) Micelles and reverse micelles with a photo and thermo double-responsive block copolymer. *J Polym Sci, Part A: Polym Chem* 48:2855–2861
- Jin Q, Liu GY, Liu XS (2010b) Photo-responsive supramolecular self-assembly and disassembly of an azobenzene-containing block copolymer. *Soft Matter* 6:5589–5595
- Johnson JA, Lu YY, Burt AO et al (2011) Core-clickable PEG-branch-azide bivalent-bottle-brush polymers by ROMP: grafting-through and clicking-to. *J Am Chem Soc* 133:559–566
- Kumar S, Allard JF, Morris D et al (2012) Near-infrared light sensitive polypeptide block copolymer micelles for drug delivery. *J Mater Chem* 22:7252–7257
- Lee H, Wu W, Oh JK et al (2007) Light-induced reversible formation of polymeric micelles. *Angew Chem Int Ed* 46:2453–2457
- Li YM, Qian YF, Liu T et al (2012a) Light-triggered concomitant enhancement of magnetic resonance imaging contrast performance and drug release rate of functionalized amphiphilic diblock copolymer micelles. *Biomacromolecules* 13:3877–3886
- Li WY, Wang YX, Chen LN et al (2012b) Light-regulated host–guest interaction as a new strategy for intracellular PEG-detachable polyplexes to facilitate nuclear entry. *Chem Commun* 48:10126–10128
- Li Y, Gao GH, Lee DS (2013) Stimulus-Sensitive polymeric nanoparticles and their applications as drug and gene carriers. *Adv Healthcare Mater* 2:388–417
- Liu GY, Chen CJ, Li DD et al (2012) Near-infrared light-sensitive micelles for enhanced intracellular drug delivery. *J Mater Chem* 22:16865–16871
- Liu G, Liu W, Dong CM (2013) UV- and NIR-responsive polymeric nanomedicines for on-demand drug delivery. *Polym Chem* 4:3431–3443
- Meng LL, Huang W, Wang DL et al (2013) Chitosan-based nanocarriers with pH and light dual response for anticancer drug delivery. *Biomacromolecules* 14:2601–2610
- Mynar JL, Goodwin AP, Cohen JA et al (2007) Two-photon degradable supramolecular assemblies of linear-dendritic copolymers. *Chem Commun* 43:2081–2082
- Pasparakis G, Manouras T, Argitis P et al (2012) Photodegradable polymers for biotechnological applications. *Macromol Rapid Commun* 33:183–198
- Rapport N (2007) Physical stimuli-responsive polymeric micelles for anti-cancer drug delivery. *Prog Polym Sci* 32:962–990
- Sailor MJ, Park JH (2012) Hybrid nanoparticles for detection and treatment of cancer. *Adv Mater* 24:3779–3802
- Srinivas G, Harikrishna D, Aliasgar S (2008) A review of stimuli-responsive nanocarriers for drug and gene delivery. *J Control Release* 126:187–204

- Sun L, Yang Y, Dong CM et al (2011) Two-photon-sensitive and sugar-targeted nanocarriers from degradable and dendritic amphiphiles. *Small* 7:401–406
- Sun L, Ma XF, Dong CM et al (2012) NIR-responsive and lectin-binding doxorubicin-loaded nanomedicine from janus-type dendritic PAMAM amphiphiles. *Biomacromolecules* 13:3581–3591
- Tamai N, Miyasaka H (2000) Ultrafast dynamics of photochromic systems. *Chem Rev* 100:1875–1890
- Trenor SR, Shultz AR, Love BJ et al (2004) Coumarins in polymers: from light harvesting to photo-cross-linkable tissue scaffolds. *Chem Rev* 104:3059–3078
- Wan XJ, Liu T, Hu JM et al (2013) Photo-degradable, protein-polyelectrolyte complex-coated, mesoporous silica nanoparticles for controlled co-release of protein and model drugs. *Macromol Rapid Commun* 34:341–347
- Wang YP, Ma N, Wang ZQ et al (2007) Photocontrolled Reversible Supramolecular Assemblies of an Azobenzene-Containing Surfactant with  $\alpha$ -Cyclodextrin. *Angew Chem Int Ed* 46:2823–2826
- Wei H, Zhuo RX, Zhang XZ (2013) Design and development of polymeric micelles with cleavable links for intracellular drug delivery. *Prog Polym Sci* 38:503–535
- Weissleder R (2001) A clearer vision for in vivo imaging. *Nature Biotechnol* 19:316–317
- Xiao W, Chen WH, Xu XD et al (2011) Design of a cellular-uptake-shielding “plug and play” template for photo controllable drug release. *Adv Mater* 23:3526–3530
- Yan B, Boyer JC, Branda NR et al (2011) Near-infrared light-triggered dissociation of block copolymer micelles using upconverting nanoparticles. *J Am Chem Soc* 133:19714–19717
- Yang YM, Shao Q, Deng RR et al (2012) In vitro and in vivo uncaging and bioluminescence imaging by using photocaged upconversion nanoparticles. *Angew Chem Int Ed* 51:3152–3159
- Yang YM, Liu F, Liu XG et al (2013) NIR light controlled photorelease of siRNA and its targeted intracellular delivery based on upconversion nanoparticles. *Nanoscale* 5:231–238
- Yesilyurt V, Ramireddy R, Thayumanava S (2011) Photoregulated release of noncovalent guests from dendritic amphiphilic nanocontainers. *Angew Chem Int Ed* 50:3038–3042