Photo-Responsive Materials for Drug Delivery System

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Abstract. Recently, much research has focused on photo-responsive materials since the responsiveness of materials is convenient to control. The application of photo-responsive materials in drug delivery is widely reported. The o-nitrobenzyl group and coumarin group are two common functional groups that can respond to lights. The *o*-nitrobenzyl group is photo-cleavable and responds to 365 nm UV lights, while the coumarin group is both photo-cleavable and photo-dimerizable and responds to lights with various wavelengths. The dimerization process of the coumarin group is reversible. Materials based on these two groups are also easy to be prepared. In this review, photo-responsive materials for drug delivery systems are introduced. The whole delivery strategy for each work will be described in detail. All delivery systems show good drug-releasing ability in light stimuli in vitro. Due to limited experiment data, the effectiveness of the delivery system in vivo cannot be determined. The near-infrared ray responsive coumarin group-based materials are more recommended due to the better penetrability of near-infrared rays.

Keywords: Photo-responsive, *o*-nitrobenzyl derivatives, coumarin derivatives, drug delivery.

1. Introduction

The development of stimuli-responsive materials has greatly enriched the design strategy of functional materials. Numerous stimuli-responsive strategies have been developed (like pH, temperature, lights, etc.) [1]. Photo-responsive strategy is quite attractive since light stimuli can be given anytime, anywhere outside of the system [2]. These features enable photo-responsive materials to be widely applied in the biomedical field [3]. The *o*-nitrobenzyl group and coumarin group are two common photo-responsive functional groups. *o*-nitrobenzyl group is a photo-cleavable group. The desired leaving group (e. g. drugs, backbone of the polymer) and residues will be disassociated under UV lights. The typical wavelength of the light is 365 nm [4]. Coumarin group is also photo-cleavable. The leaving group and residues will be disassociated under the light with a wavelength of more than 365 nm. The coumarin group can also cause a reversible dimerization reaction under various lights. The detailed photo reaction process is shown in Figure 1. Researchers have developed some drug delivery systems based on photo-responsive materials. This review will introduce some commonly used photo-responsive materials focusing on the whole delivery process.

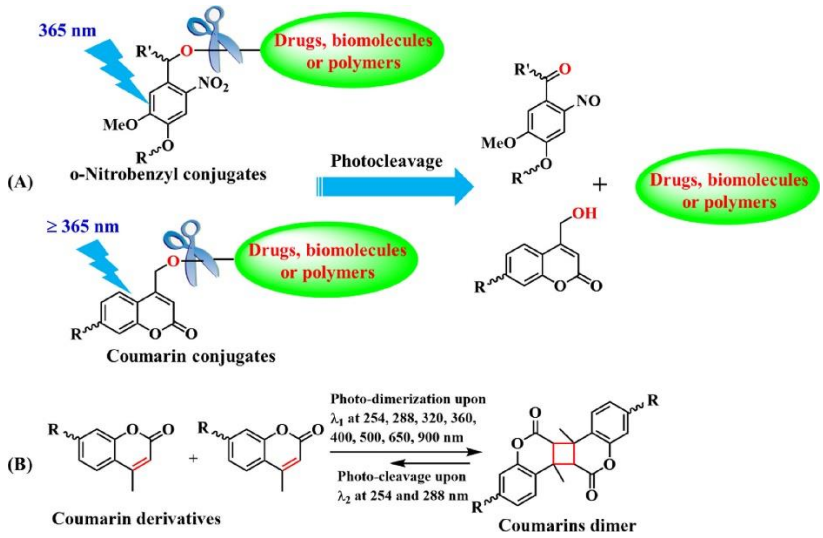

Fig. 1 Photo reaction of the (a) *o*-Nitrobenzyl group, and (b) coumarin group [4].

2. *o*-Nitrobenzyl derivatives based photo-responsive materials

2.1. Drug modification

Zhao and his team developed photo-responsive polymeric micelles based on an ABA amphiphilic triblock polymer for drug-controlled release [5]. The polymer is polylactide-*b*-*o*-nitrobenzyl-poly (ethylene glycol)-*o*-nitrobenzyl-b-poly lactide (PLA-NB-PEG-NB-PLA). With *o*-nitrobenzyl added in the junction point, PLA-NB-PEG-NB-PLA showed an excellent photo-degradation behavior. PLA-NB-PEG-NB-PLA can self-assemble into flower-like micelles in an aqueous solution, with a hydrophilic PEG block at the outer layer [5]. The PLA block can form a hydrophobic core that can load the hydrophobic drugs (DOX). Under the ultraviolet light of 365 nm, PLA-NB-PEG-NB-PLA will quickly degrade into blocks and release the loaded DOX, see Figure 2. PLA-NB-PEG-NB-PLA with different molecular weights is prepared to draw a detailed conclusion. The diameter of nano micelles increases with the increase of molecular weight, but the drug encapsulation efficiency decreases. The micelles formed with the smallest molecular weight of PLA-NB-PEG-NB-PLA show the highest photolysis rate and drug release efficiency in vitro. The in vitro cytotoxicity of the micelles is low according to the MTT assay.

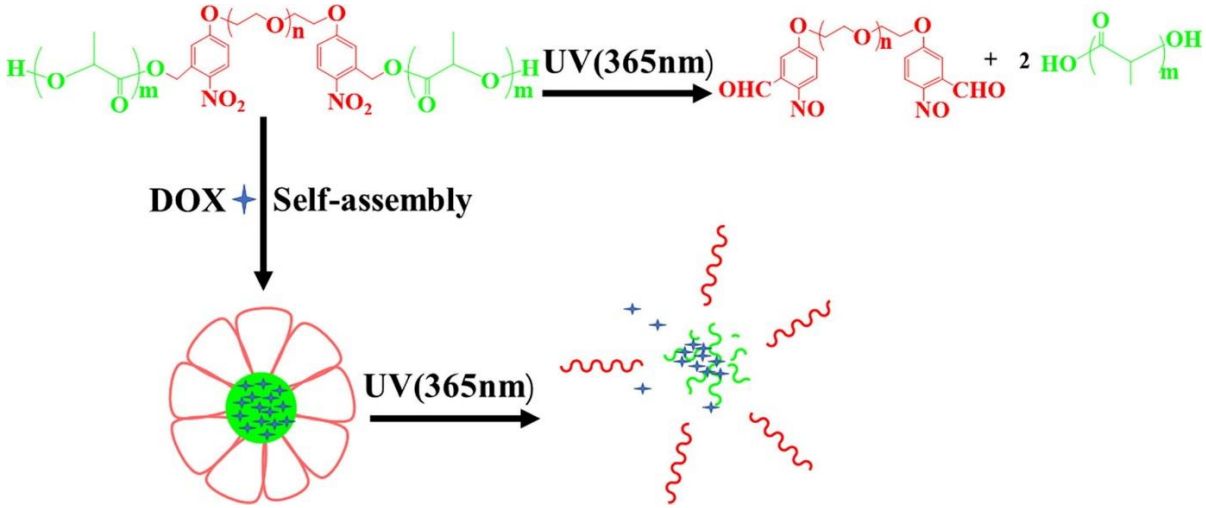

Fig. 2 PLA-NB-PEG-NB-PLA micelles drug loading and photo-responsive release [5].

Ma and his team developed a photo-oxidation-reduction triple-stimuli-responsive core-crosslinked micelles [6]. The amphiphilic block copolymers methoxy poly(ethylene glycol)-*b*-poly(3-azido-2-hydroxy-propyl methacrylate-*co*-*o*-nitrobenzyl methacrylate) [mPEG-b-P(GMA-N_3-*co*-NBM)] can self-assemble into micelles, similar to previously described work. The hydrophobic P(GMA-N_3-*co*-NBM) block forms a non-crosslinked core which is not that stable. With the azide group in P(GMA-N_3-*co*-NBM), an alkyne-functionalized agent can help to produce a more stable crosslinked core through an azide-alkyne click chemistry reaction [6]. *o*-nitrobenzyl group is at the end of the polymer side chain. It will drop under the ultraviolet light, and the end of the side chain changes to the hydrophilic carboxyl group. This change of hydrophilicity leads to the release of the loaded hydrophobic drug, Nile Red in this case. There is a disulfide bond on the alkyne-functionalized agent. The disulfide bond will be disassociated under oxidative or reductive conditions, which leads to de-crosslinking, making it easier for drug release. In combination with the o-nitrobenzyl group and disulfide bond, the triple-stimuli-responsive micelles for drug delivery are made, see Figure 3. A 6 h drug release was done to illustrate the advantage of core crosslinking and triple-stimuli-response. The result shows that core crosslinking increased the stability of micelles, and the 6 h release percentage decreased from about 15% (non-crosslinked) to about 5% (crosslinked). For the multiple stimuli-response, the UV-H_2O_2 (photo-oxidation) stimuli condition and UV-DTT (photo-reduction) stimuli show a 6 h release percentage of about 75%, while other single stimuli conditions only released no more than 60% of Nile Red [6]. Other considerations like cytotoxicity are not given in the article.

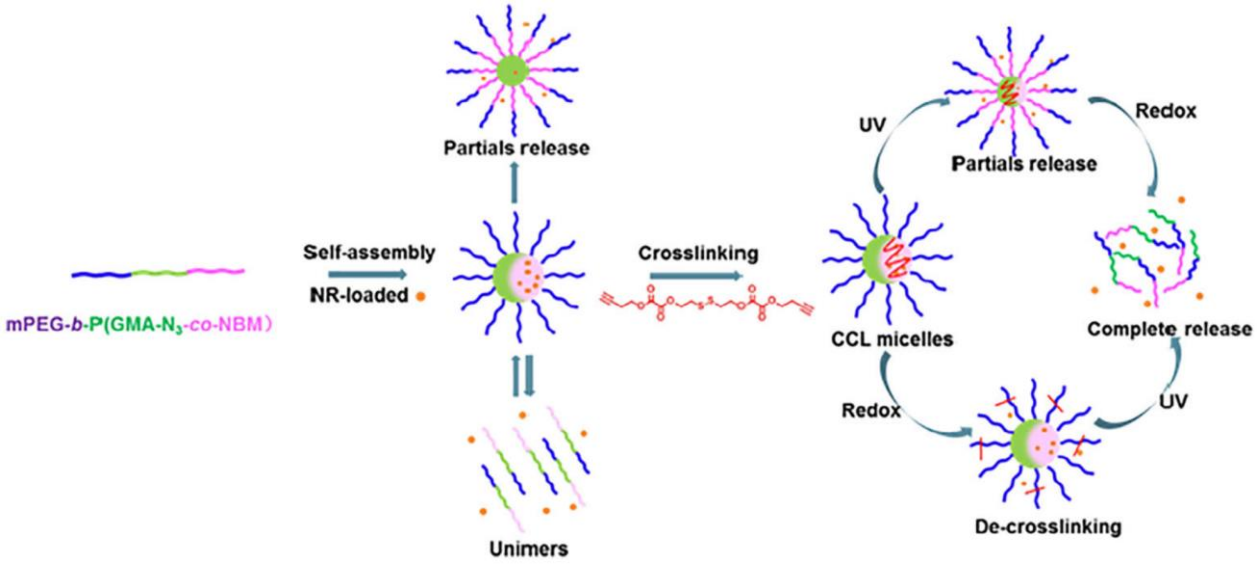

Fig. 3 Illustration of preparation and drug release of triple-stimuli-responsive micelles [6].

2.2. Hydrogels for drug delivery based on o-nitrobenzyl derivatives

Shuai and his team developed a photo-thermal dual-stimuli-responsive hydrogel based on ABA triblock polymer [7]. Two similar polymers are prepared to make the hydrogel system. The normal one is poly(ε-caprolactone)-*b*-poly(ethylene glycol)-*b*-poly(ε-caprolactone) (PCL-PEG-PCL). With the addition of the o-nitrobenzyl group at the junction point, the photo-responsive poly(ε-caprolactone)-*b*-*o*-nitrobenzyl-poly(ethylene glycol)-*o*-nitrobenzyl-*b*-poly(ε-caprolactone) (PCL-NB-PEG-NB-PCL) are made [7]. Polymers are dissolved in water to form sols, at room temperature (298.15 K). When the temperature increases, a thermal-induced phase transition occurs, and sols will turn to hydrogels. However, if it continues to increase, the system will turn back to turbid sols again. The temperature segment that the system in the hydrogel phase is called the gel-window [7]. Gel-window can be regulated by changing the concentration of polymer. Unlike other chemical reaction-induced sol-gel transitions, this thermal-induced gelation process is a completely reversible physical process. In sol state, the polymer can form micelles with hydrophobic NB-PCL core and hydrophilic PEG shell, dispersed in water. When temperature increases, the hydrogen bond between the PEG segment and water breaks up, resulting in the aggregation of polymers to form gel [7]. The turbid sol state is possibly caused by the increased molecular translation due to high temperature. Changing the hydrophilicity of the polymer can also significantly change the gel-window. The researchers prepared three different blend systems with 15wt% to 30wt% addition polymer and found that the blending of two different polymers can reduce the gel-window to physiological conditions. Plus, the increase of hydrophobic segment in the photo-responsive polymer can also decrease the gel-window. The photo-responsive behavior of the hydrogel system is also tested. The blending system of P1/P5 (20 wt%) was irradiated by 365 nm ultraviolet for 3 h. As shown in Figure 4, the hydrogel was transformed to a flowable state after irradiation [7]. This thermal-induced sol-gel transition process and photo-degradable behavior make it a potential injectable drug delivery system. Other considerations like biodegradability, loading and releasing properties, and cytotoxicity are not determined yet.

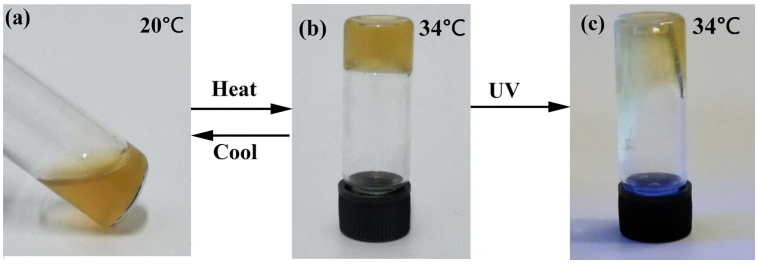

Fig. 4 Phase transition of P1/P5 system (20 wt%) [7].

3. Coumarin derivatives-based photo-responsive materials

3.1. Nanoparticles for drug delivery based on coumarin derivatives

Pashaei-Sarnaghi and his team developed a drug delivery system based on coumarin-anchored poly amidoamine (PAMAM) dendrimer nanoparticles [8]. The PAMAM dendrimer has a polar amino group (-NH_2) at the end. They are modified with coumarin derivatives. The modified dendrimer is called D-CM. Then D-CM is irradiated with 365 nm ultraviolet light, and the dimerization reaction occurs (crosslinked). Then they self-assembled into nanoparticles, and hydrophobic DOX is loaded, see Figure 5 [8]. This system can release the loaded DOX under 254 nm ultraviolet light. The release ability is tested in non-crosslinked, crosslinked, and breaking of crosslinks by 254 nm light under solutions with pH=1 (acid) and pH=7.4 (physiological condition) respectively [8]. The release ability is better in an acid solution. All crosslinked D-CM released about 10% during 72 h. With the increase in modified coumarin derivatives, the release ability decreases, because the hydrophobic coumarin derivative residues can stabilize the dendrimer-DOX system. It is worth noting that, the non-crosslinked samples always show a better release ability than the breaking one. The report said that the de-dimerization is reversible in 254 nm light, so the dimerized coumarin could not completely break down to release the DOX at a higher percentage [8]. The trends are similar in physiological conditions, but the release percentage is quite low, none of them can release more than 14% of loaded DOX [8].

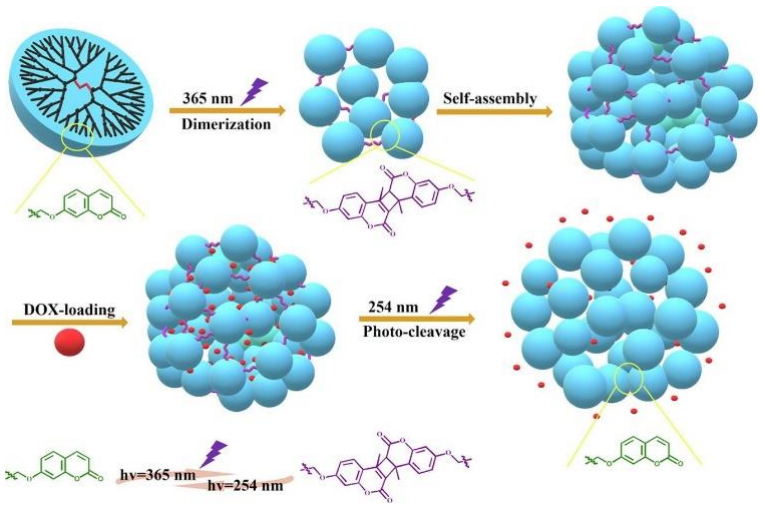

Fig. 5 Illustration of preparation and drug release of D-CM [8].

Arjmand et al. developed a photo-responsive nanoparticle based on polymer with a coumarin-based crosslinker [9]. The polymer is prepared by distillation precipitation polymerization. The photo-responsive crosslinker is first prepared. Then, with the addition of monomer 2-hydroxyethyl methacrylate (HEMA) and initiator 2,2'-Azobis(2-methylpropionitrile) (AIBN), the polymerization occurs. For the whole process Figure 6, DOX is loaded by the dialysis method. 15mg polymer and 2.4ul triethylamine are added to 1.6ml HCl-DOX solution (1.2 mg/mL). The solution is sonicated for 15 min and stirred for 24 hours at room temperature in the dark. A polymer with a non-photo-responsive crosslinker (N, N′- methylene bisacrylamide (MBA)) is also prepared. The release ability test at the physiological condition (37 °C, pH=7.4) shows a low release percentage without light stimuli. The photo-responsive polymer nanoparticles show better stability than MBA crosslinked ones [9]. Only about 5% of DOX is released after 48h experiment. While MBA crosslinked polymer nanoparticles released about 15%. Under the irradiation of 254 nm ultraviolet light, the release percentage increased to 30-35% [9]. An acid solution can reduce the stability of the nanoparticle to increase the release percentile. MTT assay showed that two kinds of nanoparticles have low cytotoxicity at low concentrations. At a concentration of 10 μg/mL, cell viability is no less than 85% after 48 h. However, the photo-responsive polymer nanoparticles have higher toxicity than MBA cross-linked ones [9].

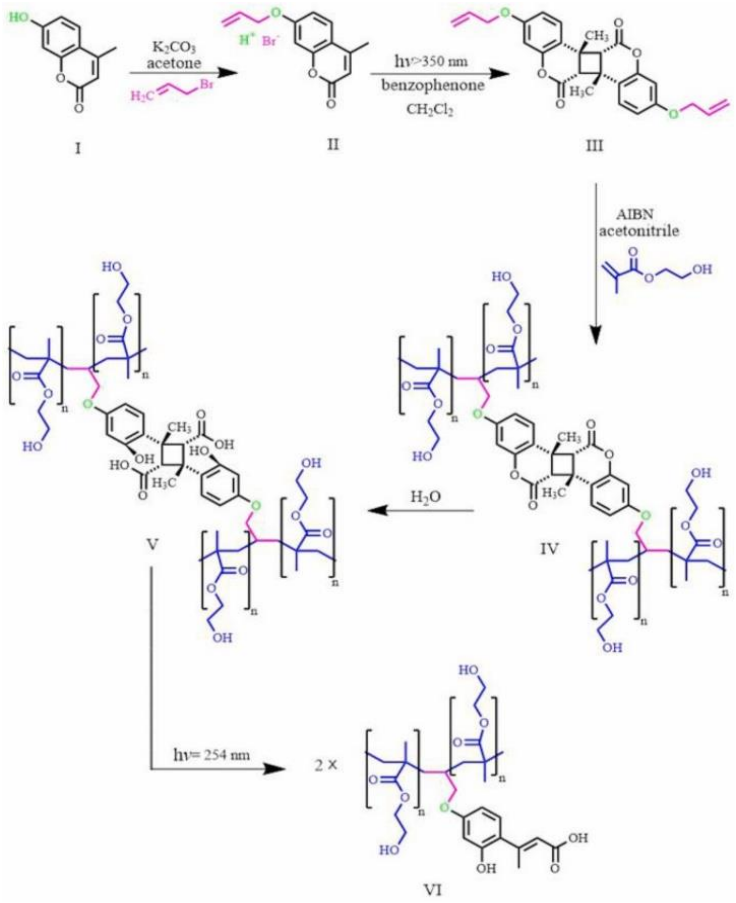

Fig. 6 Illustration of preparation and drug release of photo-responsive nanoparticle based on polymer with a coumarin-based crosslinker [9].

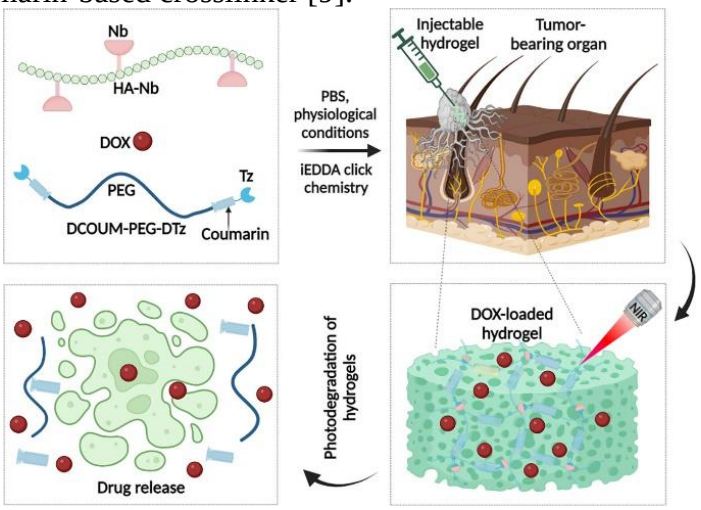

Fig. 7 Illustration of preparation and drug release of near-infrared ray responsive hydrogel [10].

3.2. Hydrogels for drug delivery based on coumarin derivatives

Gulfam and his team developed a near-infrared ray-responsive biocompatible hydrogel for drug delivery [10]. The hydrogel is derived from hyaluronic acid (HA) and coumarin-modified crosslinker. The crosslinker has a PEG backbone, with a modified NIR responsive coumarin group and terminal tetrazine (Tz) group (DCOUM-PEG-DTz). The hyaluronic acid is modified by norbornene (Nb). DCOUM-PEG-DTz crosslinker and HA-Nb are connected by Tz-Nb inverse electron demand Diels–Alder reaction when mixing in physiological conditions [10]. To load the DOX in the hydrogel, the DOX solution must be added before cross-linking. Finally, with the irradiation of NIR light, the DCOUM-PEG-DTz linker cleavage irreversibly releases the loaded DOX. The whole process is

shown in Figure 7. Three different samples with different Nb: Tz ratios are prepared. Nb:Tz=100:25 sample coded HACOUM-25, Nb:Tz=100:50 sample coded HACOUM-50, Nb:Tz=100:100 sample coded HACOUM-100 [10]. Both HACOUM-50 and HACOUM-100 show good drug loading efficiencies (more than 95%), but HACOUM-25 failed to load the DOX. During 72 h release assessment, HACOUM-50 and HACOUM-100 both showed good release ability under NIR light, HACOUM-50 released almost all loaded DOX, and HACOUM-100 released more than 50%. However, when NIR is off, HACOUMs can also release a certain degree of DOX (HACOUM-50 released 40%, HACOUM-100 released 30%) [10]. The components of the hydrogel system also show good biocompatibility, HA-Nb solution under 2000ug/mL has almost 100% cell viability, and DCOUM-PEG-DTz solution under 1000ug/ml is more than 90%. HACOUM-50 and HACOUM-100 show good biocompatibility as well, and the HACOUM-50 has less cytotoxicity [10].

4. Conclusion

Photo-responsive materials provide a brand-new approach to drug delivery. Numerous delivery systems based on *o*-Nitrobenzyl groups and coumarin groups have been developed and show good loading and releasing ability in in vitro experiments. However, few in vivo experiments are reported. The penetrability of lights must be considered for in vivo experiments or applications. Compared to the *o*-Nitrobenzyl group-based system, the system based on the coumarin group has a longer wavelength of responsive light (near infrared ray), which means it can respond to lights in deeper tissue. In future development, more experiments must be conducted. Coumarin group-based materials are more recommended due to the better penetrability of near-infrared rays.

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