Chem Soc Rev

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TUTORIAL REVIEW

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Photo-responsive block copolymer micelles: design and behavior

Cite this: DOI: 10.1039/c3cs35469e

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Received 16th November 2012

DOI: 10.1039/c3cs35469e

www.rsc.org/csr

Stimuli-responsive block copolymer micelles are the topic of intense research since they are able to show sharp and eventually reversible responses to various environmental changes and find applications in various fields including controlled drug delivery. Among all the available stimuli, light has recently 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 tutorial review, we highlight the progress realized in recent years. More precisely, we provide some guidelines towards the rational design of photo-responsive block copolymers and we present the different photo-responsive moieties that have been used so far. We also discuss the different types of irreversible and reversible responses encountered by photo-responsive block copolymer micelles. Finally, we suggest possible future developments including the design of biocompatible systems operating at excitation wavelengths compatible for biomedical applications.

Key learning points

In this tutorial review, we are providing the following clues to the reader:

1. How to select the right photo-responsive group for the right application?
2. What are the typical photo-responsive groups that can respond in a reversible or irreversible manner to light?
3. How to design photo-responsive block copolymers for either photo-induced micelle disruption or formation?
4. How to reversibly or irreversibly stabilize by photo-crosslinking one specific compartment of a micelle?
5. What are the critical issues met while designing photo-responsive block copolymer micelles for controlled drug delivery applications?

1. Introduction

Stimuli-responsive polymers have become a major topic of interest for polymer scientists. The stimuli-responsive character is usually defined as the ability of the system to undergo sharp responses to environmental changes such as pH, temperature, light, redox or chemical changes.[1] Stimuli-responsive polymers have been widely incorporated into block copolymer architectures. In most systems, a single stimuli-responsive block has been incorporated in the block copolymer but multi-responsive systems have also emerged in which different blocks can be addressed separately with the same or distinct stimuli, eventually in an orthogonal manner.[2] Such systems may find application in diverse fields including catalysis, templates, logic gates, sensors, *etc.* but the main motivation remains their potential use for drug delivery applications.[3] Among the available stimuli, light has attracted much attention since it can be localized in time and space, and it can also be triggered from outside of the system. Indeed, photo-processes usually start or stop when the light is switched on or off and they do not require particular reagents limiting byproducts. Moreover, a lot of parameters such as the intensity and the wavelength of light can be adjusted during the reaction time that enables good control over the reaction. There are several reviews that appeared recently either totally or in part dedicated to this topic, in which more exhaustive overviews of the literature are provided.[4–8] The motivation of the present tutorial review is to provide some clues for the scientists who search information for the rational design of a photo-responsive block copolymer (PRBCP) for a specific application in solution. After discussing the current understanding of PRBCPs, we want to share reflections about the possible future developments. Finally, it should be stressed that we will restrict the discussion to micellar structures formed by PRBCPs, while other types of photo-responsive polymers and materials in the bulk will not be covered.

Different types of photo-responsive micelles can be designed depending on the type of the photo-responsive group and its

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Table 1 Characteristic features of the PRBCPs discussed in this review. ATRP: atom transfer radical polymerization; ROP: ring opening polymerization; SGP: step-growth polymerization; FRP: free radical polymerization; RAFT: reversible addition–fragmentation chain transfer polymerization; AP: anionic polymerization

Photoresponsive group	Reversibility	Effect of light	Polymer block design	Polymerization technique
Pyrenylmethyl ester	No	Photocleavage	Side-chain[10]	ATRP[10]
o-Nitrobenzyl ester	No	Photocleavage	Side-chain[9,12,15,23,24,49,50] main-chain[16,17,43,44] and at the block junction[18,20–22,37]	ATRP,[9,12,18,20,22–24,37,49] ROP,[15,18,21,50] and SGP[16,17,43,44]
Coumarinyl ester	No	Photocleavage	Side-chain[11,48]	ATRP[11,48]
p-Methoxy-phenacyl ester	No	Photocleavage	Side-chain[13,14]	ATRP[13,14]
Dithienylethene	Yes	Photoisomerization	Side-chain[8]	FRP[8]
Azobenzene	Yes	Photoisomerization	Side-chain[25–31,46] and at the block junction[33]	ATRP,[25,26,29,31,46] RAFT[28,30,33] and ROP[33]
Spiropyran	Yes	Photoisomerization	Side-chain[32,47]	ATRP[32] and ROP[47]
Cinnamic ester	No	Photocycloaddition	Side-chain[35–37]	AP[35,36] and ATRP[37]
Coumarin	Yes	Photocycloaddition	Side-chain[38–41]	ATRP[38–40] and RAFT[41]
Truxillic acid	Yes	Photocycloaddition	At the block junction[19]	ATRP[19]

location in the accordingly formed micelles. For example, the photo-responsive moieties can be in principle either introduced in the micellar core, in the micellar corona or at the core–corona interface, although they have been mainly incorporated into the micellar core up to date. They can respond in a reversible or irreversible way when light is applied. In the case of an irreversible response, the incorporation of the photocleavable units in the main-chain of one of the blocks will then induce the selective degradation of a specific micellar compartment. Finally, they can also induce crosslinking of selected compartments of the micelle. All those situations will be discussed in the next sections.

In order to provide the reader a general overview of the different PRBCPs discussed in this review, Table 1 summarizes the different photo-responsive groups. The reversible character and the effect of light on each photo-responsive group are then presented. The design of each PRBCP is also described emphasizing the location of the photo-responsive group (as side-chain, incorporated in the main chain or included as a single group at the block junction) in the corresponding PRBCP. Finally, the polymerization techniques used to synthesize PRBCPs are listed.

2. Irreversible light-induced disruption of micelles

The main envisioned application of PRBCPs is light-controlled drug delivery.[4–8] Light can indeed penetrate to a certain extent into the skin and could be therefore used as a very convenient stimulus to deliver a drug at a given moment in a very precise area. The mostly investigated design for such a system is a block copolymer micelle containing the drug encapsulated into a photo-responsive hydrophobic micellar core (Fig. 1). Application of light should result in the reversible or irreversible transformation of the hydrophobic blocks into either hydrophilic ones or blocks with a significantly higher polarity. This shift in the hydrophilic–hydrophobic balance should be sufficient to transform the initial amphiphilic block copolymer into a double hydrophilic one or at least to result in a significant

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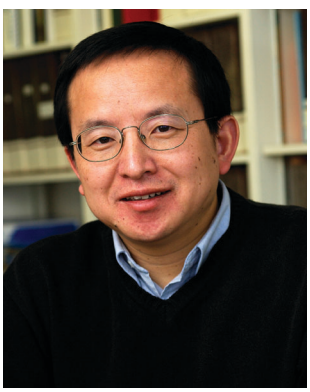
Jean-François Gohy got his PhD from Prof. Robert Jérôme's group (University of Liège, Belgium) in 1999. He then got a "Chargé de Recherches" position from the Belgian National Foundation for Scientific Research (FNRS) in the same group. In 2001–2002, he was post-doc in the group of Prof. Ulrich S. Schubert at the Eindhoven University of Technology (The Netherlands). Since 2003, he has been a Professor at the catholic University of Louvain (Belgium) in the Institute of Condensed Matter and Nanosciences (IMCN). He is the author or co-author of more than 150 scientific papers, most of them in the field of block copolymer micelles.



Yue Zhao

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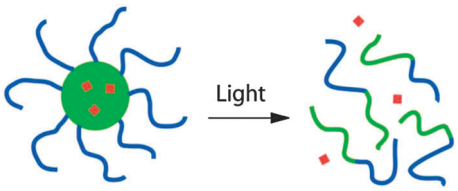

Fig. 1 Light-triggered drug release from micelles of PRBCPs. Reproduced with permission from ref. 9.

swelling of the micellar core to allow the release of the drug molecules (Fig. 1). The most common design of all the PRBCPs encountered for this application is to have one water-soluble linear block linked to an insoluble block bearing the chromophores as side groups. Besides biomedical applications, any type of molecules for a specific application could be in principle released from a light-disrupted micellar core.

Zhao and coworkers were the first to describe how to obtain irreversible light-induced disruption of aqueous micellar systems. In this respect, they have described the synthesis of diblock copolymers containing one hydrophilic poly(ethylene oxide) (PEO) sequence linked to a hydrophobic poly(methacrylate) (PMA) block bearing photo-labile side groups (Fig. 2).[9–11] Different types of photocleavable blocks have been introduced, including pyrenylmethyl esters,[10] *o*-nitrobenzyl esters[9] and esters of (diethylamino)methylcoumarinyl.[11] Those block copolymers form micelles in water with a PEO corona and a PMA core that can be further loaded with hydrophobic molecules. Light illumination induces the cleavage of the side chromophores, generating a poly(methacrylic acid) (P(*t*BA-*co*-AA)) (PMAA) block. As the resulting PEO-*b*-PMAA is fully hydrophilic, the disruption of the initial micelles and the release of the encapsulated molecules have been observed. Upon light irradiation, pyrenylmethyl esters undergo a photolysis reaction requiring the presence of water or a protonic solvent while the photocleavage of *o*-nitrobenzyl esters proceeds *via* a Norrish II type intramolecular rearrangement with no need of molecules of the solvent. Furthermore, *o*-nitrobenzyl esters undergo photocleavage upon the absorption of two near infrared (NIR) photons. This point is very crucial for biomedical applications (see later Section 8). Although the NIR photo-dissociation of *o*-nitrobenzyl containing micelles has been demonstrated, the process efficiency is much lower than with UV irradiation due to a much smaller absorption cross-section for the two NIR photons.[9] In order to address this problem, the chromophores have been changed to esters of (diethylamino)methylcoumarinyl which have the merit to feature a larger two-photon absorption cross-section.[11]

Combining light with other stimuli significantly broadens the scope of applications of such micellar systems. In this respect, *o*-nitrobenzyl groups have been introduced in temperature-responsive polymer blocks showing a lower critical solution temperature (LCST) behavior.[12] The shift in hydrophilicity induced by the photocleavage of the *o*-nitrobenzyl moieties is expected to increase the LCST in this system. More precisely a poly(ethylene oxide)-*block*-poly(ethoxytri-(ethyleneglycol)acrylate-*co*-*o*-nitrobenzylacrylate) (PEO-*b*-P(ETEGA-*co*-NBA)) block copolymer has been prepared. The PETEGA-*co*-NBA sequence is characterized by a LCST at 25 °C ($LCST_1$). The photocleavage of the *o*-nitrobenzyl esters into carboxylic acids makes PETEGA more hydrophilic and consequently increases the LCST by more than 10 °C ($LCST_2$ = 36 °C) (Fig. 3).

Light-responsiveness can also be coupled to other stimuli as recently demonstrated by Gohy and coworkers with a poly(*p*-methoxyphenacyl methacrylate)-*block*-poly((oligo ethylene glycol)methacrylate) diblock copolymer (PMPMA-*b*-POEGMA). *p*-Methoxyphenacyl esters are comparable to *o*-nitrobenzyl esters but have the advantage of not containing nitro groups. Therefore, their polymerization by controlled radical polymerization is possible, *e.g.* by atom-transfer radical polymerization (ATRP).[13] PMPMA-*b*-POEGMA copolymers form micelles with a

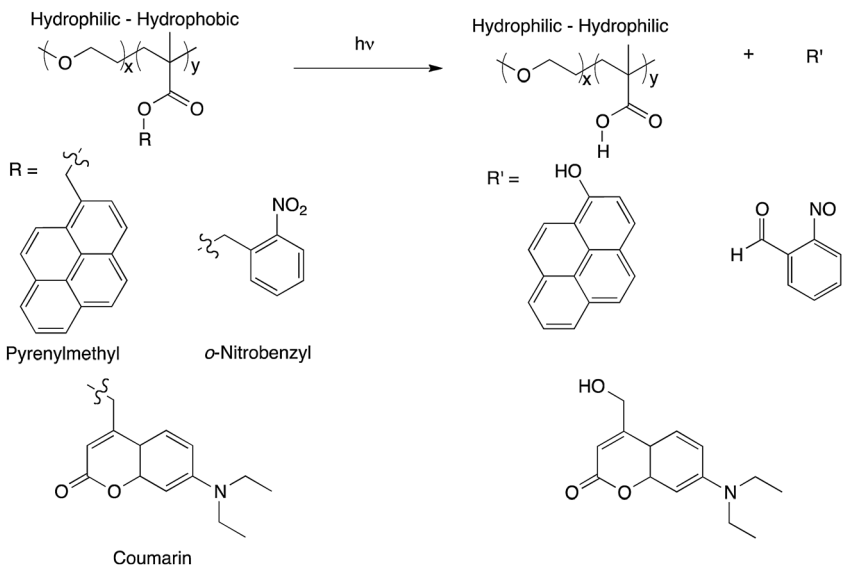

Fig. 2 Different types of photocleavable esters that have been employed for the irreversible light-induced disruption of aqueous micelles.

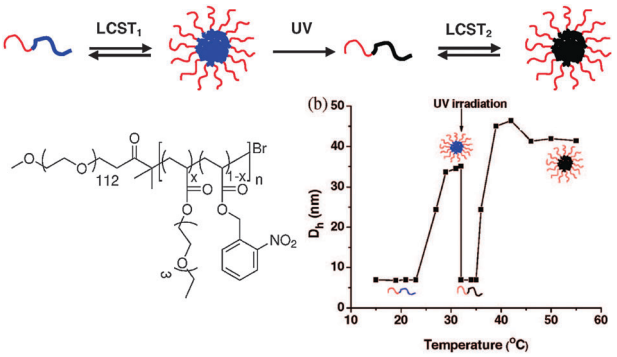

Fig. 3 Tuning the LCST in a photo-responsive PEO-*b*-P(ETEGA-*co*-NBA) (up). Chemical structure of the PEO-*b*-P(ETEGA-*co*-NBA) copolymer (left). Change in the hydrodynamic diameter (D_h) upon temperature increase and light illumination (right). Adapted from ref. 12.

PMPMA core and a POEGMA corona in water. Light irradiation leads to the transformation of PMPMA into PMAA and to the disruption of the initial micelles. The resulting PMAA-*b*-POEGMA copolymers show multi-responsive behavior to pH and calcium ions while addressing the PMAA block and to temperature (because of the LCST of POEGMA) and phosphate (PO_4^{3-}) ions due to the specific responses of the POEGMA blocks (Fig. 4).[14]

It is important to mention that the shift in hydrophilicity of the core-forming block is not always sufficient to induce a complete disruption of the initial micelles. Indeed, swelling or modifications in the characteristic size of micellar compartments as well as morphological transitions may result from the photocleavage process. Moreover, the photocleavage process may be incomplete and results in a system with a substantial amount of non-photocleaved moieties. Finally, the magnitude of the photo-induced change is also related to other parameters such as the initial composition (block length ratio) as well as the chain length (molar mass) of the starting PRBCP. Other characteristic features such as the kinetics of chain reorganization, which might be considerably slow down in the case of high glass transition "frozen" micellar cores could also play a crucial role. A typical example in which photocleavage does not lead to the disruption of micelles has been reported by Liu and Dong for PRBCPs containing a poly(amino acid) block bearing photocleavable *o*-nitrobenzyl esters.[15] Those authors have synthesized a poly(*S*-(-*o*-nitrobenzyl)-L-cysteine)-*block*-PEO diblock copolymer that forms spherical micellar structures in water. After photocleavage of the *o*-nitrobenzyl moieties, shrinkage of the micellar core was monitored. The experiment was repeated with the micelles loaded with the anticancer drug doxorubicin and the gradual release of this drug was monitored as a function of the irradiation time.[15]

Instead of having photocleavable moieties as side-chain units of the hydrophobic core-forming blocks, they can be inserted repeatedly into the main chain of the same block. In this case, photo-irradiation results in the disappearance of the micellar core due to main-chain degradation of the core-forming blocks. Fast photodegradation of the micelles can be achieved with this design, which might be of interest for dedicated applications. This approach has been recently documented for ABA triblock copolymers containing PEO as hydrophilic A outer blocks and a central B block prepared by polycondensation and integrating photocleavable *o*-nitrobenzyl groups.[16] Micelles with a core of B and a corona of A have been prepared from this block copolymer. Under UV irradiation, fast degradation of the micellar core and hence micelle disruption were observed. In the case of a B core loaded with a molecule of interest, its burst release was observed. In the next paper, the design of this type of ABA triblock copolymer was fine-tuned by incorporating both redox-cleavable disulfide groups and photocleavable *o*-nitrobenzyl groups in the

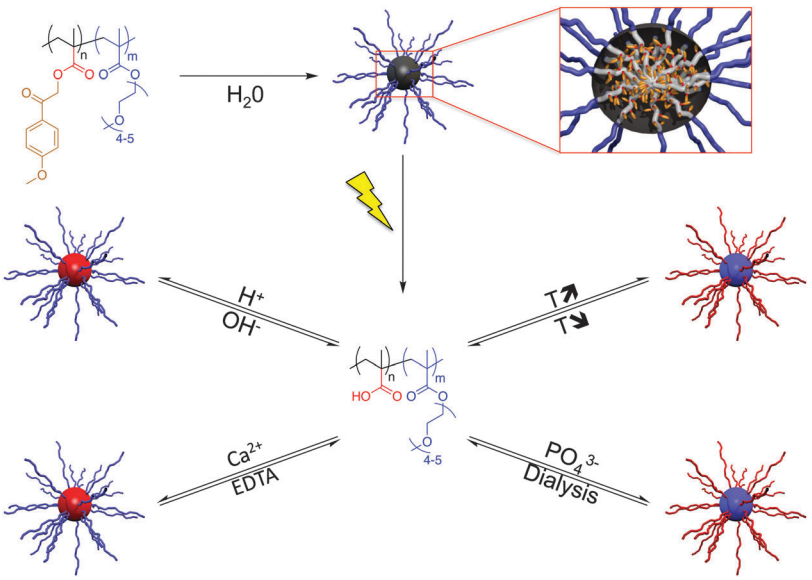

Fig. 4 A multi-responsive micellar system based on poly(*p*-methoxyphenacyl methacrylate)-*block*-poly((oligo ethylene glycol)methacrylate) diblock copolymers (EDTA: ethylenediaminetetraacetic acid sodium salt). Reprinted with permission from ref. 14.

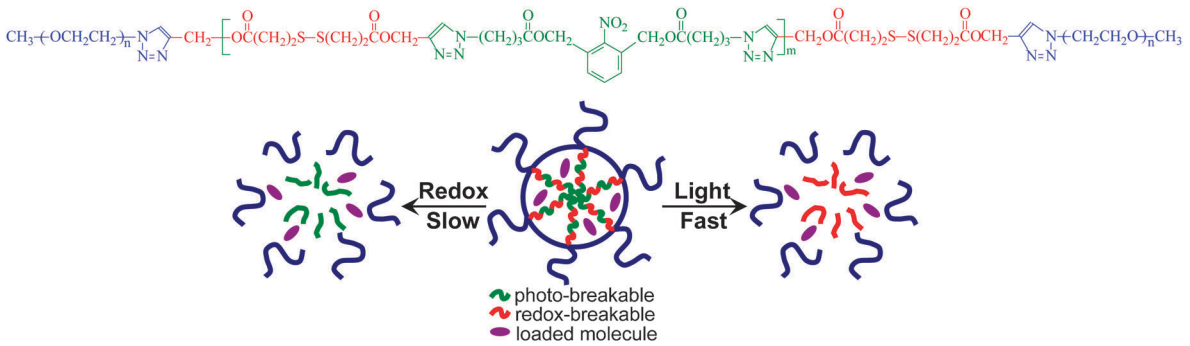

Fig. 5 Chemical structure (top) of a redox and photocleavable PRBCP allowing either slow redox-triggered or fast light-triggered disruption of micelles (bottom). Adapted with permission from ref. 17.

main chain of the hydrophobic middle block using click condensation (Fig. 5).[17] The idea was to obtain a micellar system that could undergo irreversible disruption upon application of the adequate stimuli. Interestingly enough, while irradiation of the micelles resulted in a rapid disruption of the micelles thanks to fast photocleavage of the *o*-nitrobenzyl groups, addition of a reducing agent slowly cleaved the disulfide bonds. This feature makes possible either burst release of an encapsulated agent through UV light irradiation or slow release by the action of a reducing agent, or release with concomitant fast and slow profiles using the two stimuli (Fig. 5).

A final strategy towards irreversible light-induced disruption of micelles consists in introducing a single photocleavable group between the core and corona forming block of the PRBCP. The principle of operation of such systems is however somewhat different from the photocleavable block copolymer micelles discussed above since the photoreaction does not result in the direct disruption of the micellar core. Indeed, light liberates the coronal chains from the micellar cores that tend to aggregate and precipitate out from the solution due to the lack of steric stabilization. This approach has been documented for amphiphilic diblock copolymers incorporating either *o*-nitrobenzyl esters[18] or truxillic acid[19] derivatives at the block junction (Fig. 6). The main challenge in this approach is to design synthetic strategies allowing for specifically introducing in high yield the photocleavable group at the block junction. An interesting synthetic route consists then in ''clicking'' a photocleavable ATRP initiator on an end-functionalized azide block while the second block is simultaneously polymerized by ATRP.[20]

From the designing point of view, this approach is not best suited for the controlled release of core-encapsulated molecules. However, it could be interesting to use it for the photo-induced destabilization of vesicles. In this respect, the removal of coronal chains in vesicles obtained from such block copolymers with photocleavable junctions results in the destabilization of the vesicular wall, the subsequent breaking of the vesicles into small hydrophobic parts and finally the release of molecules initially encapsulated in the vesicles. Indeed, recent reports have clearly demonstrated the validity of this approach. For example, Katz and coworkers have designed biocompatible block copolymers

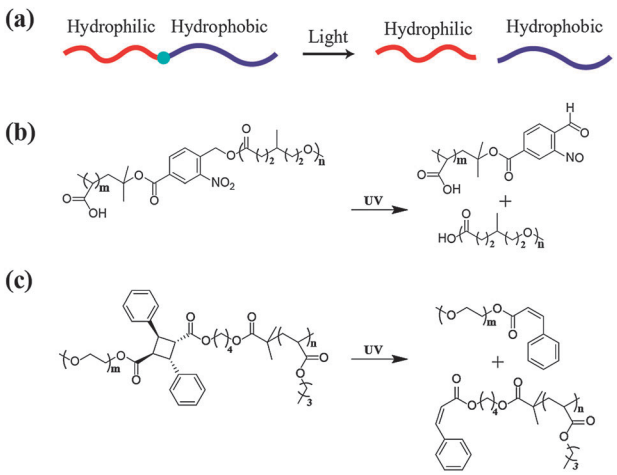

Fig. 6 Block copolymers with a photocleavable junction between the blocks (a). Examples of such structures based on *o*-nitrobenzyl ester (b) and truxillic acid (c) derivatives.

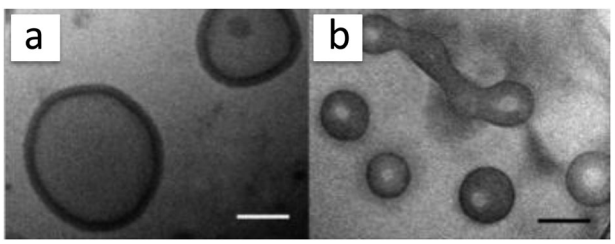

Fig. 7 Cryo-TEM images of polymersomes prepared from PCL-*b*-PEO copolymers with a 2-nitrophenylalanine group at the block junction (a) before and (b) after 6 h of UV exposure. Scale bars = 100 nm. Adapted with permission from ref. 21.

comprising a poly(ε-caprolactone) (PCL) and a PEO block.[21] They succeeded to introduce a photo-labile 2-nitrophenylalanine group at the junction between the PCL and PEO blocks. The accordingly synthesized copolymers were able to form polymersomes in water and were loaded with biocytin. Upon photocleavage of the *o*-nitrobenzyl groups, the bilayer membrane of the initial polymersome was disturbed and a re-organization towards smaller polymersomes was observed accompanied by the release of the

initially encapsulated biocytin (Fig. 7). A similar approach was used by Meier and coworkers to prepare light-responsive polymersomes able to deliver a variety of payloads including drugs, proteins, enzymes and DNA.[22]

3. Irreversible light-induced formation of micelles

Light can be also used to irreversibly induce the formation of micelles instead of disrupting them. This strategy has been rarely used compared to light-induced disruption of micelles but could be of high interest when the sequestration of a molecule from the surrounding solution is requested. Basically, the starting component in this approach is a block copolymer in a non-selective solvent. Upon irradiation, one of the blocks will experience a shift in polarity that should be sufficient to render this block insoluble in the surrounding medium and further induce the formation of micellar structures. In the photocleavable moieties depicted in Fig. 2, it is obvious that light transforms a hydrophobic group into a hydrophilic one. Thus, if one employs those photocleavable groups, reverse micelles in an apolar solvent can be targeted. In this case, the initial PRBCP is a double hydrophobic block copolymer that, upon light irradiation, transforms into an amphiphilic system in which the hydrophilic block aggregates into micellar cores in the apolar solvent. Molecules presenting a polar character could be encapsulated into the core by using this approach. This strategy has been documented by Gohy and coworkers for copolymers constituted of a polystyrene (PS) block and either a poly(*o*-nitrobenzylacrylate) (PNBA)[23] or a poly(dimethoxy-*o*-nitrobenzylacrylate) (PDMNBA)[24] photocleavable block. In chloroform, those block copolymers are dissolved as unimers. However, irradiation at 300 nm (for PNBA) or at 350 nm (for PDMNBA) results in the photocleavage of the *o*-nitrobenzyl esters in PNBA or PDMNBA, respectively. This results in the transformation of the initial hydrophobic PNBA and PDMNBA blocks into hydrophilic PAA. Therefore the initial double hydrophobic PS-*b*-PNBA and PS-*b*-PDMNBA diblock copolymers turn into amphiphilic PS-*b*-PAA systems upon irradiation at the proper wavelength. Aggregation of the poorly soluble PAA blocks in chloroform finally results in reverse micelles with a PAA core and a PS corona. This photo-driven micellization process can be advantageously used to encapsulate molecules of interest. The concept has been demonstrated by using a fluorescent coumarin derivative during the micellization process (Fig. 8). This dye bears a tertiary amine group and is able to interact with the carboxylic acid moieties of PAA. Moreover, the photo-driven encapsulation process has been demonstrated to be more efficient than the diffusion-controlled encapsulation realized by simply adding the dye to a solution of chloroform containing the preformed PS-*b*-PAA reverse micelles.

That no suitable system for micellization in aqueous media has been reported so far remains the main limitation to irreversible light-induced formation of micelles. Indeed, all the photocleavable moieties used up to now are characterized by the transformation of a hydrophobic group into a hydrophilic carboxylic acid. Irreversible photo-induced transformation of a hydrophilic group into a hydrophobic one remains a challenge for future research.

4. Reversible light-induced disruption or formation of micelles

The shift in the hydrophilic–hydrophobic balance needed to induce micelle disruption can be designed in a reversible manner.

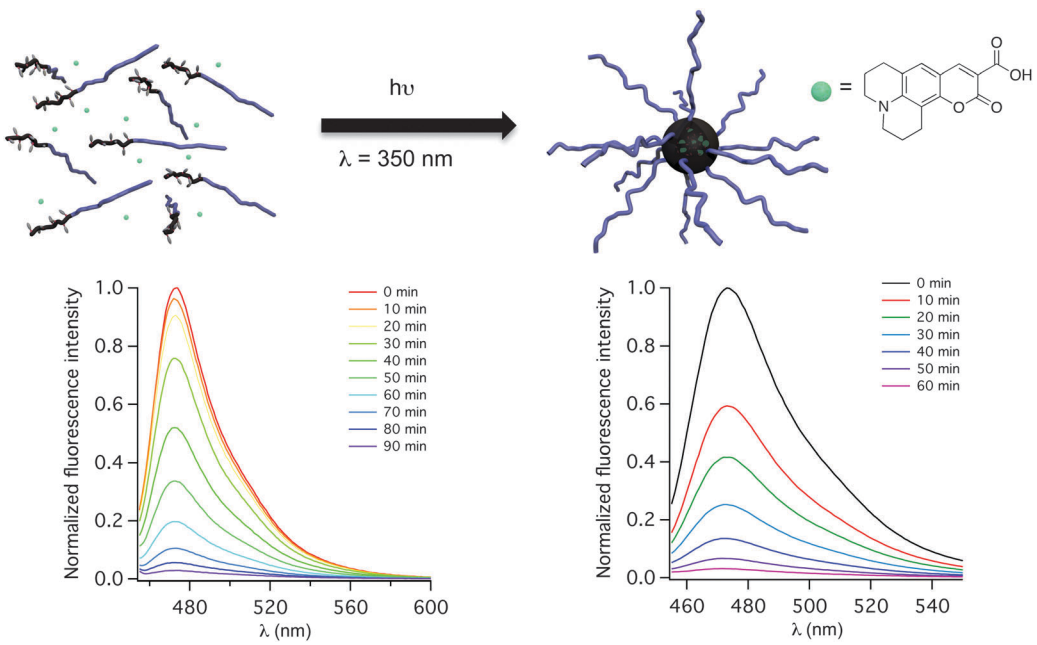

Fig. 8 Schematic representation of photo-induced micellization and concomitant sequestration of a coumarin dye for PS-*b*-PNBA and PS-*b*-PDMNBA diblock copolymers in chloroform (top). Evolution of the coumarin dye fluorescence intensity as a function of irradiation time for PS-*b*-PNBA (bottom, left, reproduced with permission from ref. 23) and PS-*b*-PDMNBA (bottom, right, reproduced from ref. 24).

Due to its reversible character, it is clear that such an approach allows not only micelle disruption but also micelle formation. Although this strategy seems to be more powerful than the irreversible disruption of micelles, the enthusiasm has to be tempered by the fact that the shift in the hydrophilic or hydrophobic character in reversibly photo-responding groups is usually much weaker than for irreversible systems. Moreover, the slow kinetics at which the photoactive moieties respond to light or relax to their initial state in the absence of light could be a severe limitation to their use in practical applications. Finally, the reversibility is generally not achieved since the initial characteristic features of the system are usually not fully recovered during irradiation cycles. Several photochromic molecules have been used for this design, including azobenzene, spiropyran and dithienylethene (Fig. 9). Those groups are characterized by a reversible photoisomerization reaction upon irradiation to UV or visible light.

Among the different groups able to modify their hydrophobic or hydrophilic character upon irradiation, azobenzenes and their derivatives constitute by far the most studied reversible photo-responsive motif. The principle of operation of azobenzenes is the reversible *trans–cis* photoisomerization of their nitrogen–nitrogen double bond (N=N). In this process, the apolar *trans* isomer can be converted to the polar *cis* one upon UV light irradiation while the back isomerization can be triggered by visible light. This reversible photoisomerization process has been used by Zhao and coworkers to design a micellar system that is disrupted upon UV irradiation and reforms itself when irradiated with visible light.[25,26] This system is based on a diblock copolymer (Fig. 9a) containing on one side a hydrophilic random poly(*t*-butyl acrylate-*co*-acrylic acid) (P(*t*BA-*co*-AA)) block and on the other side a poly(methacrylate) bearing azobenzenes as pendent groups (PMAz). Spherical micelles and/or vesicles have been observed from this copolymer dissolved in a dioxane–water mixture depending on the water content. Upon UV irradiation, the azobenzene side-chain groups in the apolar *trans* form (dipole moment ~0 D) were converted to the polar *cis* form (dipole moment ~4.4 D), increasing the polarity of the PMAz block and resulting in the disruption of the micellar aggregates. Subsequently, when visible light was applied, azobenzene groups isomerized back to the *trans* form and the micellar aggregates reformed. The reversibility of this process was confirmed by monitoring the optical transmittance of a low power laser (λ = 633 nm) through the micellar solution (Fig. 10). Multi-responsive systems combining response to light and to another stimulus have also been successfully designed. An example is a PRBCP in which the hydrophobic block is an azobenzene-containing thermo-sensitive polymer having a LCST.[27] In this case, the polarity change induced by the photoisomerization of azobenzenes could shift the LCST and determine the assembly or disassembly of block copolymer chains at a given solution temperature.

As stated above, the shift in the hydrophilic–hydrophobic balance in azobenzene-containing PRBCPs might be not sufficient to induce micelle formation or disruption. It could rather induce a deformation or even a morphological transition for the irradiated micellar aggregates.[28–31] As a typical example, polymersomes obtained in THF/water (50/50 vol%) from a poly(*N*-isopropylacrylamide)-*block*-poly(acrylate) copolymer bearing azobenzenes as side-groups (PNIPAM-*b*-PAz) experienced a fusion process triggered by

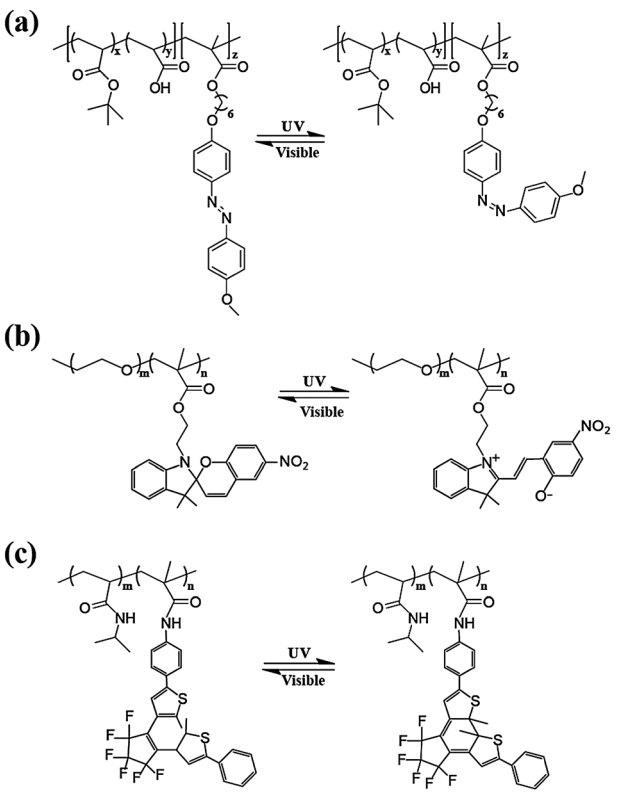

Fig. 9 Examples of block copolymer structures using different types of photoisomerizable groups for the reversible light-induced disruption or formation of aqueous micelles: (a) azobenzene, (b) spiropyran and (c) dithienylethene. For each group, both photoisomers are shown.

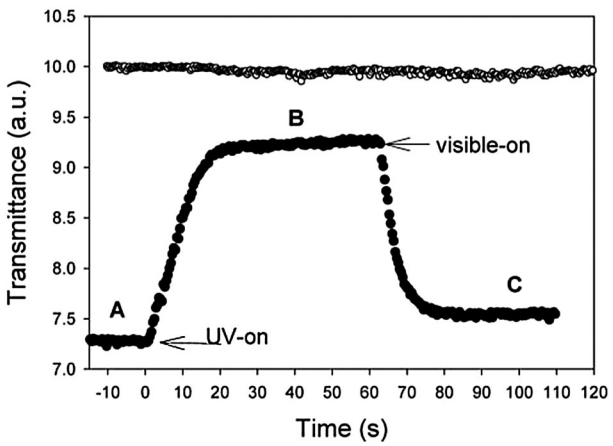

Fig. 10 Changes in the transmittance for P(*t*BA-*co*-AA)-*b*-PMAz vesicles before irradiation with UV light (A), after UV irradiation (B) and after exposure to visible light (C), indicating the reversible dissociation and formation of the vesicles. The transmittance of the fully solubilized diblock in dioxane subjected to the same UV and visible light irradiation is also shown (line at ~10 a.u.). Reproduced with permission from ref. 26.

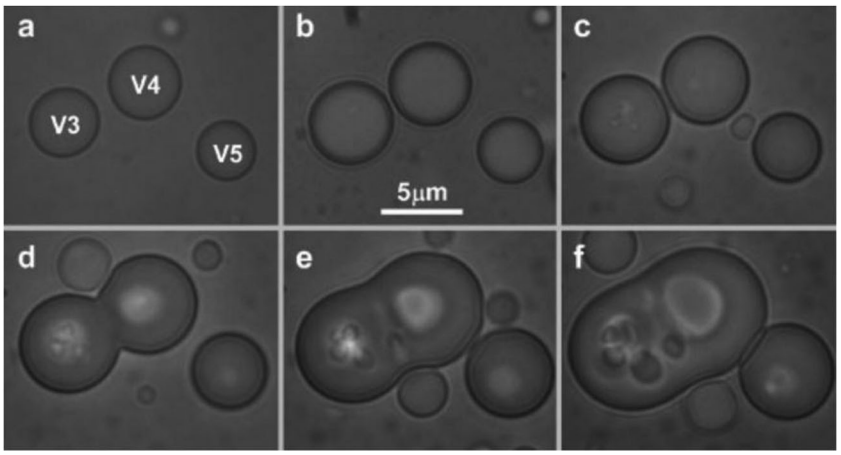

Fig. 11 Photo-induced fusion of PNIPAM-*b*-PAz vesicles. Initial vesicles (a) and vesicles observed after irradiation of 16 (b), 33 (c), 42 (d), 58 (e) and 80 min (f). Reproduced with permission from ref. 28.

photo-irradiation.[28] Fusion occurred as soon as the polymersomes were exposed to UV light (Fig. 11). Indeed, the *trans*-to-*cis* isomerization not only increases the hydrophilicity of the *trans* azobenzenes but also disturbs their packing in the vesicular membrane creating defects. The associated surface expansion increases surface free energy and fusion of vesicles appears to be the most likely way to reduce that excess of free energy and to stabilize the objects.

Other promising photo-sensitive groups for reversible formation or disruption of micelles are hydrophobic spiropyrans that undergo photoisomerization into their hydrophilic zwitterionic merocyanine forms upon UV irradiation while the reverse process is triggered by visible light (620 nm). The shift in the hydrophilic–hydrophobic balance is larger than that with azobenzenes and therefore makes spiropyran-containing PRBCPs valuable precursors for reversible light-induced formation and disruption of micelles. This approach has been used by Matyjaszewski and coworkers with a poly(ethylene oxide)-*block*-poly(methacrylate) whose methacrylate block is bearing spiropyran (SP) side-chains (PEO-*b*-PMSP).[32] Micelle disruption was observed upon irradiation of the PEO-*b*-PMSP micelles in water due to the photo-induced conversion of neutral spiropyran to charged merocyanine. Moreover, this system was successfully used for the encapsulation and release of molecules. In this respect, a coumarin dye was initially encapsulated in micelles made of the PEO-*b*-PMSP and then released upon excitation at 365 nm. The partial re-incorporation of the fluorescent dyes was then triggered by visible light (up to almost 50% of re-encapsulation of released dye molecules).[32]

Again, all the previous examples of reversible PRBCPs discussed in this section involve many photo-responsive moieties attached as pendent groups on a polymer backbone. Although PRBCP architectures containing photocleavable block junctions are well known, as discussed in Section 2 for irreversible photo-responsive systems, it is challenging to obtain a single photo-reactive block junction that can reversibly link and detach two blocks under light exposure at two different wavelengths. This has been achieved by Yuan and coworkers by making use of an inclusion complex between an azobenzene group and a cyclodextrin (CD) positioned at one chain end of a PAA block and at one chain end of a PCL block, respectively.[33] Complexation is effective between the *trans* isomer of the azobenzene and CD under visible light, forming the diblock copolymer while the bent *cis* isomer is expulsed from the CD cavity under UV light, separating the two blocks. With such a design, the PCL-*b*-PAA diblock copolymer can form or dissociate depending on the illumination conditions.

5. Irreversible photo-induced crosslinking of micelles

The stabilization of micelles *via* the crosslinking of either their core or corona is a topic of high interest.[34] Since micelles are dynamic structures that disintegrate themselves below their critical micelle concentration, crosslinking is the easiest way to stabilize those structures, which might be a prerequisite for some applications. Among the different methods allowing micellar crosslinking, light-induced crosslinking is a valuable tool since chemical reagents and unwanted byproducts are avoided.

Light-induced crosslinking of micelles and vesicles was first reported by Liu and coworkers who used the [2 + 2] photocycloaddition of cinnamic esters for photo-crosslinking.[35,36] A typical example illustrating this strategy is shown in Fig. 12 in which the membranes of vesicles made of polyisoprene-*block*-poly(2-cinnamoylethyl methacrylate) (PI-*b*-PCEMA) have been photo-crosslinked.[36] As the PI chains formed the outer and the inner layer of the vesicle, they could be either partially or fully removed by ozonolysis of their double bonds, which "shaves" those hairy nano-objects. Recently, Liu and coworkers combined the concepts of irreversible photo-crosslinking of cinnamic esters-containing polymer blocks and of the use of a photocleavable *o*-nitrobenzyl ester junction in the same copolymer.[37] To reach this goal, they synthesized a PEO-*block*-poly(2-(perfluorooctyl)ethyl methacrylate)-*block*-PCEMA (PEO-*b*-PFOEMA-*b*-PCEMA) triblock copolymer with a photocleavable *o*-nitrobenzyl group located in

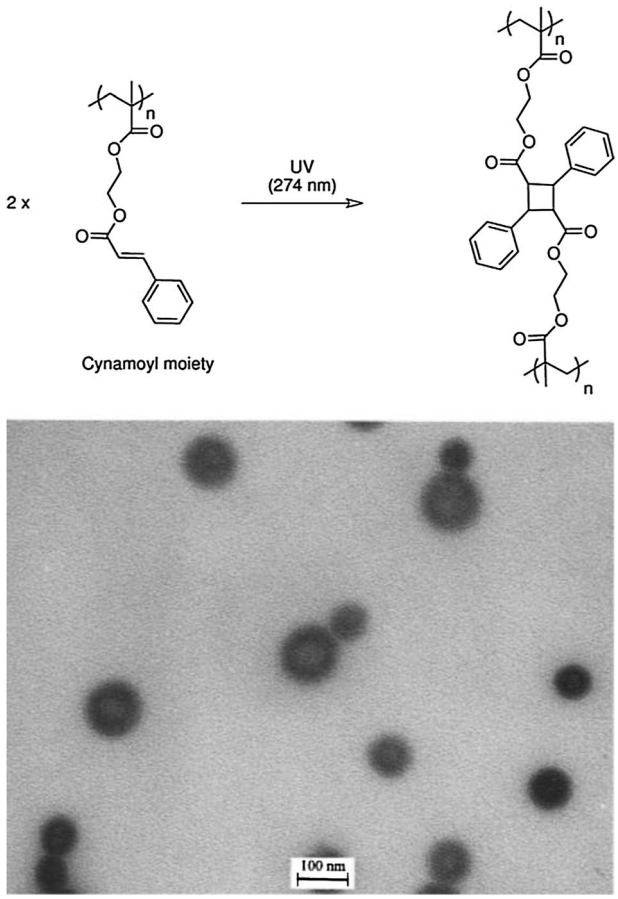

Fig. 12 Photodimerization of cinnamic esters (top). TEM picture of fully shaved nanospheres made from PI-*b*-PCEMA (down). Reproduced with permission from ref. 36.

between the PEO and PFOEMA blocks. Micelles were formed from this copolymer in a tetrahydrofuran–water 20 : 80 vol/vol mixture in which only the PEO block was soluble. Upon photolysis, the PCEMA micellar core was crosslinked and the PEO blocks were released in solution, leaving crosslinked PFOEMA-*b*-PCEMA nanoparticles exhibiting oil and water-repellant behavior.

6. Reversible photo-induced crosslinking of micelles

The reversible photo-crosslinking of micellar structures could be advantageous for some applications. For example, the release of active molecules from crosslinked cores may be difficult. Reversible crosslinking could ensure a good stability of the micelles and a limited release of the encapsulated molecules in the crosslinked state, while the non-crosslinked state could be specifically triggered to activate the delivery of the encapsulated species. Again, reversible crosslinking could be performed either in the core or the corona of the micellar objects although most studies focused on micellar core crosslinking. This strategy was explored by Zhao and coworkers who introduced coumarin derivatives in amphiphilic block copolymers in order to stabilize either the core or the shell of the accordingly formed micelles.[38,39] Coumarin moieties are indeed able to undergo a reversible [2 + 2] photocycloaddition upon UV irradiation. A copolymer composed of a water-soluble PEO block and of a poly(methacrylate) block incorporating coumarin side-chains (PCMA) was designed. Micelles with a photo-crosslinkable PCMA core and a PEO corona were formed by dissolving this copolymer in water.[38] Photo-crosslinking was triggered by irradiating the micelles at wavelengths above 310 nm while photo-de-crosslinking occurred upon irradiation at wavelengths below 260 nm. Although the photo-de-crosslinking process appeared to be incomplete, a certain degree of reversibility can be achieved as shown in Fig. 13. Moreover crosslinked micelles slow down the release of encapsulated molecules compared to the non-crosslinked ones.

Corona-photo-crosslinked micelles were also reported by Zhao and coworkers from a poly(dimethylaminoethyl methacrylate)-*block*-poly(methyl methacrylate-*random*-coumarin methacrylate) (PDMAEMA-*b*-P(MMA-*r*-CMA)).[39] Reverse micelles were first

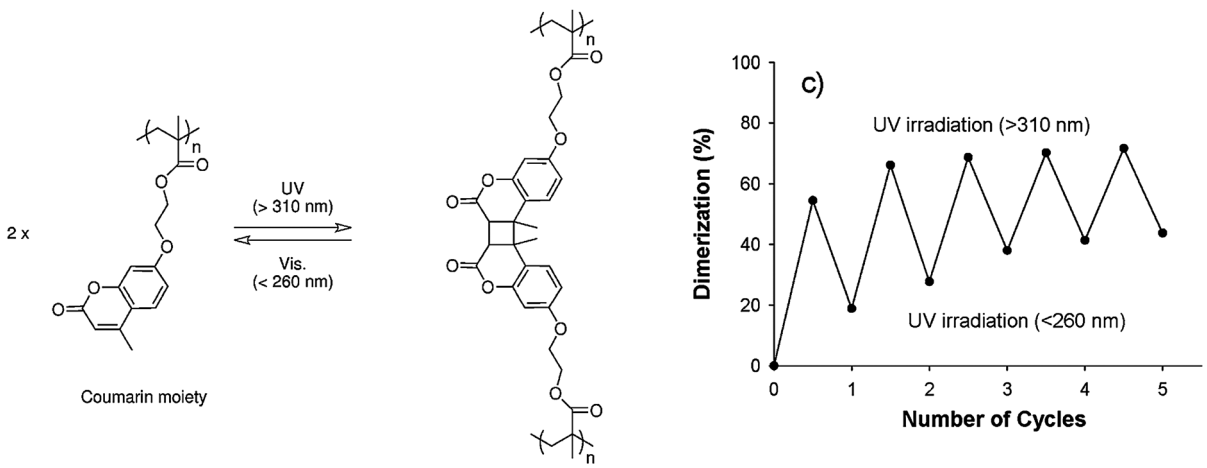

Fig. 13 Photo-induced dimerization of coumarin moieties in PCMA (left). Reversible photodimerization of the coumarin moieties in PEO-*b*-PCMA micelles exposed to alternated illuminations (right), reproduced with permission from ref. 38.

prepared in a tetrahydrofuran–dichloromethane mixture from this copolymer with the PDMAEMA blocks quaternized and consisted of a quaternized PDMAEMA core surrounded by a P(MMA-*r*-CMA) corona. The outer P(MMA-*r*-CMA) corona was then photo-crosslinked and the periphery of those micelles was further decorated by extra PDMAEMA chains grafted by a subsequent ATRP of DMAEMA initiated by chloride groups remaining at the surface of the crosslinked shell. With such a design, the final micelles contained both the core and the outer shell made of hydrophilic PDMAEMA separated by a crosslinked P(MMA-*r*-CMA) intermediate layer.

Finally, additional stimuli-responsive character can be added to reversibly photo-crosslinked micelles. The basic design to achieve this goal is to introduce one or two blocks displaying a LCST behavior for instance and bearing a small amount of coumarin derivatives as side groups for photo-crosslinking. For example, Zhao and coworkers described a diblock copolymer composed of PEO and a coumarin-containing poly(2-(2-methoxyethoxy)ethyl methacrylate) ($PMEO_2MA$) known for its LCST behavior.[40] Core-crosslinked micelles could be easily obtained from this copolymer by heating it in water above the LCST of the $PMEO_2MA$ block and by photo-crosslinking of the coumarin derivatives in the core. The crosslinking of the coumarin moieties in the core prevents dissociation of the micellar structure below the LCST of $PMEO_2MA$, giving rise to the formation of microgel nanoparticles. In addition, with the reversible photoreaction, the size of the nanoobjects can be optically controlled by tuning the degree of crosslinking which determines the swelling of the micelles.

Similarly, the same authors described large reversible volume changes in vesicles based on the same approach.[41] A copolymer formed of a coumarin-containing PDMAEMA block and a thermo-responsive poly(*N*-isopropylacrylamide) (PNIPAM) block was used in this study. Large vesicles with a PNIPAM membrane were formed in water from this copolymer above the LCST of the PNIPAM block. After photodimerization of the coumarin groups, the vesicles were cooled down below the LCST of PNIPAM and underwent expansion up to 700% due to the hydration of the PNIPAM membrane while retaining their structural integrity due to crosslinking. Interestingly enough, contraction of those vesicles occurred upon subsequent heating above the LCST of PNIPAM.

7. Future directions for photo-responsive block copolymer micelles

As highlighted in the previous sections, recent years have witnessed significant progresses in the design of PRBCPs undergoing either irreversible or reversible photo-induced processes. The advances in controlled radical polymerization techniques such as ATRP and reversible addition–fragmentation chain transfer polymerization (RAFT), which greatly facilitate the synthesis of well-defined PRBCPs with tailored functionalities and architectures, certainly helped boosting the interest of scientists and making these breakthroughs. Other polymerization techniques also contribute to these progresses such as ring-opening metathesis polymerization which has been recently used to prepare photocleavable polymers incorporating *o*-nitrobenzyl derivatives as side chains of a norbornene monomer.[42] Moreover, other recent concepts in macromolecular chemistry such as the use of ''click'' chemistry have further allowed the introduction of photo-sensitive moieties in specific locations of PRBCPs with high yield and high precision.[20]

One of the key problems in the design of PRBCPs is to obtain systems displaying large amplitude photo-induced effects. In this respect, one way to observe sharp irreversible photo-induced changes is to trigger main-chain polymer degradation *via* self-immolating chemistry. In this case, the photo-induced removal of pendent protecting groups could unmask reactive functions causing the degradation of the main-chain backbone (*e.g.* with acidolysis). This strategy has been indeed recently explored for systems in which the removal of the *o*-nitrobenzyl or coumarin protecting groups results in the degradation of polymer nanoparticles and in the subsequent burst release of encapsulated molecules.[43,44] As far as reversible photo-induced processes based on the *trans–cis* photoisomerization of azobenzenes are concerned, the photo-induced shift in the hydrophilic–hydrophobic balance remains limited. One way to increase the change in dipolar moment during the *trans–cis* isomerization consists in introducing proper substituents on the phenyl rings on the azobenzene group.[26] Another method relies on a supramolecular approach in which the azobenzene group has been utilized as a guest molecule for the CD cavity. In that approach, the *trans* form is complexed in the CD cavity while the *cis* form is freed in solution. The associated change in the hydrophilic–hydrophobic balance in that the specific case may be larger than simply playing with the *trans–cis* photoisomerization of the bare azobenzene group. This strategy has indeed been recently used to produce vesicles from a copolymer incorporating azobenzenes in the *cis* form.[45] Irradiation with visible light resulted in the complexation of the *trans* azobenzene with CD and in the breaking of the vesicles. Since the hydroxyl groups of CD can be further functionalized, its selective complexation with *trans* azobenzene can be further explored as a general strategy to amplify polarity changes in order to trigger morphological changes or disruption/formation of micellar aggregates. The *trans–cis* photoisomerization of azobenzene can also be employed to tune the liquid crystalline behavior. In this respect, the elongated *trans* isomer of azobenzene is a mesogen for the ordered mesophase to be observed, while the bent *cis* form induces disorder and triggers a transition to the isotropic state. Such transitions have been widely investigated for bulk liquid crystalline polymers containing azobenzene moieties and have been recently used to trigger burst release from vesicles.[46] In this example, a liquid crystalline polymer with azobenzene side chains has been incorporated in the vesicular wall. UV irradiation results in the photoisomerization of the *trans* azobenzene into its *cis* isomer and hence a liquid crystalline to isotropic transition in the vesicular wall. This transition essentially collapses the liquid crystalline blocks and induces a curling instability ultimately leading to the burst of the vesicular membrane.[46]

All these examples show peculiar effects of light on micellar aggregates formed by carefully and ingeniously designed PRBCPs. They also pave the way towards new designs and mechanisms of actions.

8. Use of photo-responsive block copolymer micelles for controlled drug delivery applications

It is clear that one of the key applications of micelles from PRBCPs is their use as nanocarriers for controlled drug delivery. However a careful choice of the materials used for those carriers should be done. In this respect, the biocompatible and biodegradable characteristic features are most required. While looking back on all the previous examples described so far in this tutorial review, PEO has been mostly considered as the corona-forming block. This choice is motivated by the fact that PEO is a biocompatible polymer (although this is still controversial and it depends on its molecular weight), a highly hydrophilic polymer ensuring a good steric stabilization of the nanocarriers prepared from PRBCPs and it also inhibits the adsorption of proteins on its surface thanks to the so-called "stealth" effect.

However, less attention has been paid until now on the choice of the hydrophobic blocks incorporating variable amounts of photochromic moieties, which are often belonging to the poly(methacrylate) family. Some recent studies proposed the use of poly(amino acids) sequences modified by photocleavable moieties as hydrophobic blocks for PRBCPs. In this respect, a diblock copolymer composed of a PEO block and a poly(glutamic acid) sequence containing a number of spiropyran side groups has been reported.[47] This copolymer formed micelles in aqueous medium that could be reversibly disassembled and reassembled upon irradiation to UV and visible light, respectively, because of the light triggered photoisomerization of hydrophobic spiropyran towards the more hydrophilic merocyanine form.[47]

The toxicity of the photochromic group itself and of the products of the photoreaction has to be carefully considered. For example, the toxicity of *o*-nitrobenzyl esters is poorly documented. Moreover, the products of their photodegradation contain a nitrosobenzaldehyde which not only might be toxic on its own, but also absorbs UV light and degrades further into other ill-defined products. An obvious way to get rid off the toxicity of the products of the photo-induced reaction would be to consider light-cleavable drug–PRBCP conjugates. In this way, the products of the photocleavage would be the active drugs. This approach has been largely unexplored to date. A recent example of this strategy has been reported for an anticancer drug 5-fluorouracil which has been linked covalently to coumarin side groups *via* UV-promoted cycloaddition at wavelengths above 310 nm in the hydrophobic micellar core. Further irradiation at a wavelength of 254 nm allowed the transformation of the hydrophobic drug-bearing blocks in the core into hydrophilic ones and thus in the disruption of the micelles accompanied by the release of the drug.[48]

Besides the biocompatibility and biodegradability issues, the choice of the wavelength to trigger photoreactions is also critical for biomedical applications. UV radiations are mostly used up to now to trigger either irreversible or reversible photo-induced reactions. Such radiations are problematic for biomedical applications since they might cause damages to healthy cells during their application and because their penetration into living tissues is rather limited. A solution to this problem may be found with the utilization of NIR light which is a lower energy radiation with a reduced absorption and scattering by biological media and hence deeper penetration. However the use of NIR light requires that the photocleavable moieties are able to undergo a two-photon absorption process for the same energy as the corresponding one-photon absorption in the UV or visible spectral region. This is possible for some of the photoactive groups discussed in this review (mostly coumarin derivatives) but not for all. Moreover the photoreactions induced by two-photon absorption of NIR are generally slower and inefficient due to the typically low two-photon absorption cross-sections of the chromophores. Therefore, the use of a femtosecond pulse laser is generally needed to observe significant two-photon absorption, which might be a technical limitation for applications. Interestingly enough, alternatives have recently emerged in the literature to overcome those problems. A possibility to enhance the efficiency of NIR light excitation is to use a sensitizer approach. In this respect, lanthanide-doped up-converting nanoparticles that absorb NIR light and convert it into UV or visible light might be an interesting alternative. Moreover, the use of those nanoparticles requires much lower power NIR density compared to classical NIR-triggered two-photon absorptions since their excitation occurs *via* sequential, multiple absorptions with real energy levels. In that case, the use of continuous-wave NIR radiations from a laser diode is sufficient to trigger the desired photoreactions. Using this approach, Zhao and coworkers encapsulated $NaYF_4$:TmYb up-converting nanoparticles into the *o*-nitrobenzyl-functionalized poly(methacrylate) core of aqueous block copolymer micelles loaded with model molecules.[49] The accordingly loaded micelles were exposed to NIR light at 980 nm and the photons emitted at *ca.* 350 nm by the up-converting nanoparticles were used for the irreversible photocleavage of the *o*-nitrobenzylesters. This resulted in a hydrophobic to hydrophilic shift for the core forming blocks and in the disruption of the micelles. This disruption was accompanied by the release of the initially encapsulated payloads (Fig. 14). This strategy could be used in the future to prepare other types of NIR photo-responsive micellar systems.

It should be noted that in principle the UV light emitted by up-converting nanoparticles might also cause damaging effect on surrounding tissues or biomolecules, but such an effect should be negligible. Unlike using direct UV light excitation, for which the UV beam causes damage mainly during its trip before reaching the micelles, with up-converting nanoparticles, UV light is emitted from the interior of micelles upon NIR light excitation and most of UV photons should be absorbed by surrounding photosensitive moieties in the polymer instead of interacting with biomolecules.

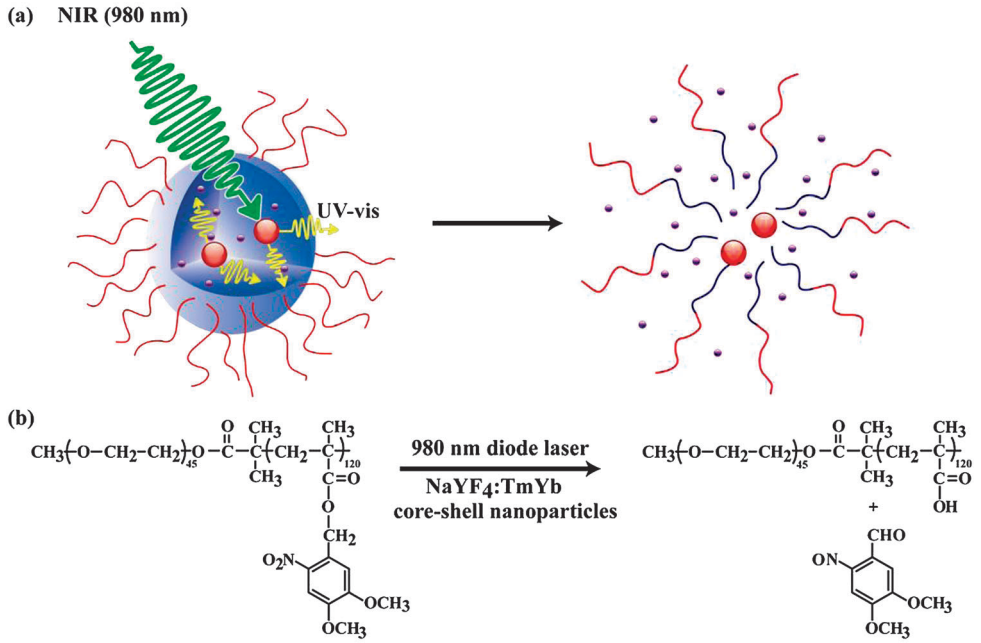

Fig. 14 (a) Schematic illustration of using NIR light excitation of up-converting nanoparticles to trigger dissociation of micelles. (b) NIR light-triggered photoreaction with the used PRBCP and $NaYF_4$:TmYb nanoparticles. Reproduced with permission from ref. 49.

The potential of PRBCPs incorporating coumarin-based chromophores for NIR activation and featuring a possibly biocompatible character was recently demonstrated by Zhao and coworkers for a PEO-*block*-poly(glutamic acid) diblock copolymer in which a number of 6-bromo-7-hydroxycoumarin-4-yl methyl groups were grafted as side chains on the poly(glutamic acid) block. Micelles with a PEO corona surrounding a core of the polypeptide block were accordingly formed in water and either an antibacterial drug (Rifampicin) or an anticancer drug (Paclitaxel) was encapsulated into the micellar core. Upon NIR illumination of those micelles at 794 nm, the disruption of the micelles was observed, together with the release of the encapsulated drugs.[50]

9. Conclusions

In this tutorial review, we have highlighted the recent progresses made in the field of photo-responsive micellar systems based on PRBCPs. We have classified the different systems based on the reversible or irreversible character of their photo-induced structural or morphological changes. We have also distinguished the systems in which light is able to cause the disruption/formation of the micellar system or to a less extent to modify its self-assembly behavior (*e.g.* morphology, rigidity of the membrane in the case of vesicles) by shifting the hydrophilic–hydrophobic balance of the PRBCPs, and the systems where light is used to stabilize the micellar structure by crosslinking. It is clear that a wide variety of photochromic moieties as well as synthetic strategies to introduce them in defined locations of macromolecular architectures are now made available to the chemist. However many challenges still need to be addressed, especially as far as applications of those systems are concerned. Up to now, biomedical applications in the field of controlled drug release have been essentially envisioned. The main limitations encountered up to now are the biodegradability and biocompatibility of the selected PRBCPs, the toxicity of the products resulting from the photo-induced reactions and the issue of the wavelength used to trigger the photoreactions. Although some interesting solutions to these issues have been recently proposed including the use of light-responsive poly(amino acids) in PRBCPs, the design of photocleavable polymer–drug conjugates as pro-drugs and the use of NIR radiations for sensitized photo-responsive micellar systems, there is still much room in the field for further developments. Other applications of micellar systems from PRBCPs are also possible in the field of cosmetic and agricultural industries, self-healing materials and smart coatings but are almost unexplored. Since the last few years have witnessed the blossoming of PRBCPs with various structures and functions, it is clear that this endeavor will continue in the near future.

Acknowledgements

JFG thanks the P2M network from the ESF and the Communauté française de Belgique for financial support in the frame of the ARC SUPRATUNE. YZ is grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and le Fonds québécois de la recherche sur la nature et les technologies of Québec (FQRNT).

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