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Review

Light-sensitive Intelligent Drug Delivery Systems†

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ABSTRACT

Drug delivery systems (DDS) capable of releasing an active molecule at the appropriate site and at a rate that adjusts in response to the progression of the disease or to certain functions/biorhythms of the organism are particularly appealing. Biocompatible materials sensitive to certain physiological variables or external physicochemical stimuli (intelligent materials) can be used for achieving this aim. Light-responsiveness is receiving increasing attention owing to the possibility of developing materials sensitive to innocuous electromagnetic radiation (mainly in the UV, visible and near-infrared range), which can be applied on demand at well delimited sites of the body. Some light-responsive DDS are of a single use (*i.e.* the light triggers an irreversible structural change that provokes the delivery of the entire dose) while others able to undergo reversible structural changes when cycles of light/dark are applied, behave as multi-switchable carriers (releasing the drug in a pulsatile manner). In this review, the mechanisms used to develop polymeric micelles, gels, liposomes and nanocomposites with light-sensitiveness are analyzed. Examples of the capability of some polymeric, lipidic and inorganic structures to regulate the release of small solutes and biomacromolecules are presented and the potential of light-sensitive carriers as functional components of intelligent DDS is discussed.

INTRODUCTION

Considerable efforts are currently being exerted to develop more efficient and safe drug delivery systems (DDS) that provide therapeutic levels of drugs in specific organs, tissues or even cellular structures, where and when required. Traditional medicines devoted to the achievement of systemic levels sufficient to reach the target by an immediate or progressive drug-flooding of the body are no longer valid for most of the emergent synthetic and biotechnological therapeutic molecules, owing to the instability and toxicity problems or to hindrances to reach the target structure from the systemic circulation (1). Furthermore, long-time used drugs could benefit greatly from the development of a discontinuous (triggered) drug release in response to a specific stimulus (2). Thus, DDS capable of releasing an active molecule at the appropriate site and at a rate that adjusts in response to the progression of the disease or to certain functions/biorhythms of the organism are particularly appealing (3,4). To bring such a vision of the responsive DDS to clinical use, the majority of efforts are directed toward integrating the biomimetic methodologies into tailor-designed drug carriers, mainly based on molecule-selective agents, camouflage coatings/shells or stimuli-sensitive components (1). Although quite complex and diverse, stimuli-responsive DDS are intended to mimic the events that occur when a cellular signal triggers a massive release of biochemical mediators from secretory granules or vesicles that serve as storage containers and undergo a reversible conformational change in response to an applied stimulus (5).

DDS that modulate drug release as a function of the specific stimuli intensity are called ''intelligent'' and can work in open or closed circuit (6–8). Closed-loop or self-regulated systems detect certain changes in biological variables (*e.g.* pH, temperature or concentration of some substances) by activating or modulating the response, *i.e.* by switching drug release on and off or automatically adjusting the release rate. On the other hand, open-loop systems can respond to specific external stimuli by releasing the drug in a pulsatile manner, commensurate with the intensity/duration of each stimulus. Such a release mode is advantageously independent of the conditions of the biological environment, enabling a precise and explicit triggering of the release. The exponential growth of publications on lipidic and polymeric architectures in the last decade or so reflects upon the development of DDS responsive to irradiation, heat, electrical or magnetic field, compression or ultrasound (9–12).

Light-responsive systems possess a potential of becoming truly biomimetic sensors or actuators (13). Photoinduced self-healing polymers can mimic the biological systems in which damage triggers a self-healing response. These materials can be used to repair fiber fracture, delamination or propagation of microcracks of polymeric components used in a variety of applications, extending the functional life and safety of the polymeric components (14,15). On the other hand, some polymers such as segmented polyurethanes that are able to undergo light-induced shape changes can imitate the

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movement of artificial muscles, the shape-memory polymers being useful for medical devices that can recover a certain form by a remote light activation (16,17). Another example of light-responsive systems is ''gated'' membranes controlling the transport of ions or the flow of gases or liquids through microchannels (18–21).

The development of biocompatible materials for *in vivo* applications and the improved understanding of the photo-regulated solute transport opened the prospects of photo-responsive materials in drug delivery (22). Electromagnetic radiation in the range of 2500–380 nm can be externally applied to the body to switch drug release on and off at a specific site, offering a potential for controlling the release that is otherwise difficult to achieve using other stimuli and reducing the effect of radiation on the adjacent tissues to a minimum (23). UV or blue light can serve as a triggering agent for topical treatments applied to the skin or the mucosa (24–26). Radiation of wavelength below 700 nm cannot penetrate more than 1 cm deep into the tissue, because of scattering and a high level of endogenous absorbers, such as oxy- and deoxy-hemoglobin, lipids and water (27,28). Thus, the interest in light irradiation below 700 nm is limited to the treatment of pathological processes on or under the skin or on the external layers of some internal organs. One of the key strategies for a deeper (more than a few millimeters) light penetration into living tissues has been the use of near-infrared (NIR) light within the range of wavelengths from 650 to 900 nm. This is because hemoglobin (the principal absorber of visible light) and water and lipids (the main absorbers of infrared light) have their lowest absorption coefficient in the NIR region (Fig. 1) (29). NIR imaging techniques are currently being used for noninvasive *in vivo* imaging of physiological, metabolic and molecular function. For instance, light with a wavelength of 830 nm is used for measurement of oxidation of hemoglobin in many organs, including the brain (30). NIR is innocuous and does not cause a significant heating in the area of its application. Therefore, such light can be useful for triggering a drug release in the difficult to access areas of the body (30–32).

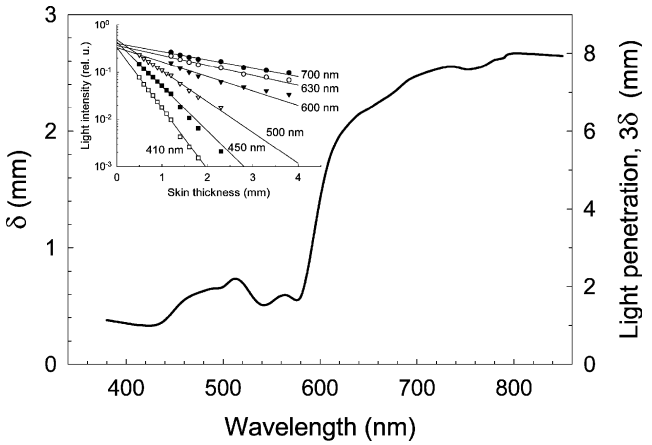

Figure 1. The penetration depth of the excitation light in the rat skin. The parameters δ and 3δ are the depths where the light intensity is reduced to 37% or 5% of the light incident on skin surface, respectively. The inset shows the exponential decay of the intensity of various wavelength lights when penetrating the skin. Intensity values extrapolated to zero were 0.3–0.5, which means that skin reflectance is 50–70%. Reproduced from Juzenas *et al.* (27) by permission of The Royal Society of Chemistry (RSC) on behalf of the European Society for Photobiology and the European Photochemistry Association.

Drug release rate regulated by the light conditions should be distinguished from two other therapeutic approaches in which light is also used as a triggering agent: photodynamic therapy and *in situ* photopolymerization leading to a formation of permanent filling materials or depots. Photodynamic therapy is intended to cause cell death and involves a photosensitizer, light and oxygen present in the tissue. Once the photosensitizer is administered to a patient, the tissue to be treated is exposed to light suitable for exciting the photosensitizer. When the photosensitizer and oxygen molecules are in close proximity, an energy transfer takes place that allows the photosensitizer to relax to its ground singlet state while creating an excited, singlet state oxygen molecule. Singlet oxygen is a very aggressive chemical species that rapidly reacts with any nearby biomolecule, provoking destructive reactions that lead to apoptosis or necrosis (33). Photopolymerizable materials used for preparing dental composites or implants such as UV-curable precursors adopting the shape of the implantation zone are applied without the use of injections or other invasive techniques. This approach has a potential for achieving prolonged delivery (yet not stimuli-responsive) of dental antiseptics or peptides and hormones (34).

Research into light-responsive DDS has been focused mainly on self-assembled colloids such as copolymer micelles and liposomes, although other photoresponsive supramolecular architectures are also under study (32,35–39). Modern laser systems enable a precise control of light wavelength, duration, intensity and diameter of the beam and offer a wide range of possibilities for biomedical applications (40). In this review, we analyze the basis of the light-controlled DDS using some selected experimental results to illustrate the current state of the art and the steps toward future applications in therapeutics.

LIGHT-RESPONSIVE MICELLES AND GELS

Surfactant and amphiphilic block copolymer (BCP) micelles are nanocarriers that have been frequently considered for controlled delivery applications (23,39,41,42). The most clearly defined concept of the micellar use as a drug delivery carrier would be a possibility of triggered carrier disruption by light exposure and subsequent drug release (Fig. 2). BCPs intended for light-controlled micelle disruption usually incorporate a chromophore into the structure of the hydrophobic block. The chromophore photoreaction results in a conformational or structural change that shifts the hydrophilic/lipophilic balance toward the destabilization of the micelles. Both reversible and irreversible dissociation of the BCP micelles upon illumination with UV/visible or NIR light have been achieved with various chromophores, including azobenzene, pyrene and nitrobenzene (39). Diverse mechanisms can be involved in the BCP destabilization phenomenon depending on the structure of the photoactive group (Fig. 3) (43). Azobenzene groups possess different dipolar moments in the *trans* and *cis* conformations (Fig. 3A); cinnamoyl groups isomerize to more hydrophilic species due to the electric charge generation or dimerization (Fig. 3B), while spirobenzopyran groups are transformed in zwitterion species (Fig. 3C).

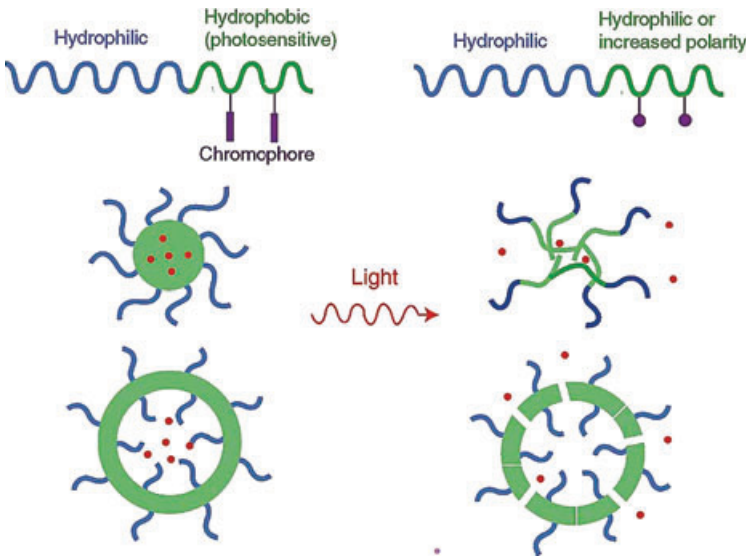

Figure 2. Schematic illustration of the rational design of light dissociable block copolymer core-shell micelles or vesicles. The photoreaction of the chromophore on the hydrophobic polymer either increases its polarity or converts it into a hydrophilic polymer; in both cases the hydrophilic/hydrophobic balance can be shifted toward the destabilization of the micellar association. Reproduced from Zhao (39) by permission of Wiley Interscience.

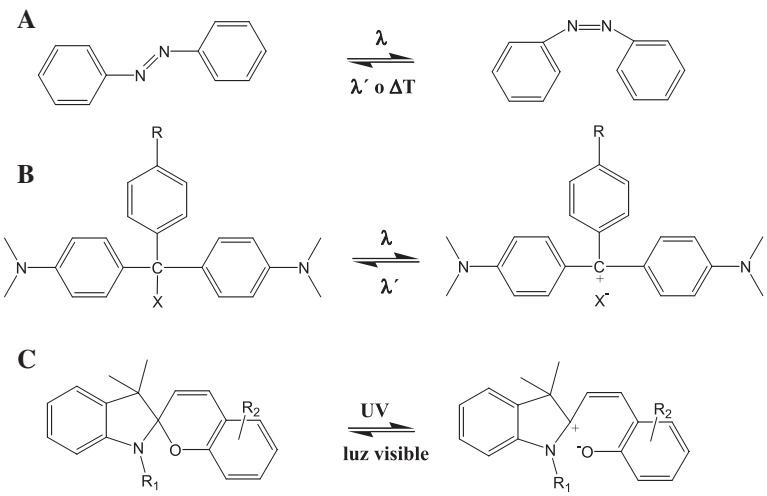

Figure 3. Effect of light irradiation on the structure of some photosensitive groups: (A) *trans*-to-*cis* isomerization, (B) ionization and (C) zwitterion formation.

Surfactants and BCP with azobenzene structural units in the lipophilic tail offer the ability to control interfacial properties uniquely, through irradiation with light of appropriate wavelengths (44–50). The planar *trans* (visible light) form of such surfactants or BCP is more hydrophobic than the nonplanar *cis* (UV light) form, and hence the critical micellization concentration, which typically correlates with the hydrophobicity of the surfactant tails, is lower for the *trans* than the *cis* isomer of the surfactant or the BCP. The wavelength that triggers the isomerization depends on the nature of the substituent groups and, thus, can be readily tuned (51). The *cis* form is unstable at the body temperature, so that in darkness or if exposed to a higher wavelength radiation, it reverts to the *trans* form. Therefore, cycles of micellar destabilization/reconstitution can be obtained by applying light pulses (52).

The conformation of the azobenzene groups also determines the intra- and inter-molecular interactions of their copolymers. Therefore, it may be possible for the surfactant molecules, predominantly in *trans* form, to aggregate under visible light irradiation. Irradiation of the *trans* form micelles with UV light causes the surfactants to adopt a more polar *cis* form, with a subsequent dissolution of the micelles. Such systems can be employed as photocontrollable polymer nanocarriers that can release loaded agents on demand and in targeted places of the human body. Copolymers of *N*,*N*-dimethylacrylamide (DMA) and methacryloyloxyazobenzene (MOAB) with pendant azobenzene moieties along the backbone exhibit a significant concentration-dependent photoviscosity effect in water, without macrophase separation. Such phenomena can be advantageously used in photoswitchable fluidic devices and in protein separation (53). Photoisomerization and

dissociation upon UV irradiation of the azobenzene groups located predominantly in the aggregates (that act as junctions connecting elastic chains) leads to a loss of viscoelasticity. The presence of aggregates that are impermeable to certain solutes such as proteins and the like can alter the overall transport through the polymer network, as the solutes should negotiate a more torturous diffusional path through the aggregate-cross-linked gel. Analogously, micelles of a cationic azobenzene-trimethylammonium bromide surfactant can act as cross-linkers of hydrophobically modified poly(acrylic acid), solubilizing the alkyl side chains of the polymer and leading to gelation (49). If the surfactant conformation changes to *cis* due to the exposure to UV light, the aggregates disappear and the viscosity decreases. Similarly, dispersions of seroalbumin and micelles of poly(acrylic acid)-1,2-aminoundecilamido-4-phenylazobenzene present a high viscosity at dark due to intra- and inter-micellar interactions, and this prevents the release of the protein. The azo groups adopt the *cis* conformation and the micelles break when irradiated with UV light. Consequently, the viscosity drops and the protein is released. If the system is kept in the dark or exposed to visible light (436 nm), the azo groups recover the *trans* conformation, the viscosity rises again and the release stops (54). These copolymers have a potential in developing protein pulsatile delivery systems (Fig. 4).

A different strategy based on the photosolvolysis of hydrophobic groups can be adopted with micellar solutions of amphiphilic BCPs whose hydrophilic block is poly(ethylene oxide) (PEO) and whose hydrophobic block is a polymethacrylate bearing pyrene moiety in the side group (52,55). UV irradiation cleaves the pyrene moiety off the polymer and converts the hydrophobic block into a hydrophilic poly(methacrylic acid) (PMA). The micelles that are no longer stabilized by the hydrophobic associations dissociate because of the repulsive interactions between the charged PMA segments. Copolymers bearing chromophores that can be photolyzed by NIR light have been also developed (23). BCPs of PEO and poly(2-nitrobenzyl methacrylate) undergo the photolysis of 2-nitrobenzyl moieties, *via* either one-photon UV (365 nm) or two-photon NIR (700 nm) absorption, also transforming the hydrophobic block into hydrophilic PMA. The release of a hydrophobic dye, Nile Red, from the photolabile polymer micelles became faster as the irradiation intensity increased, because of the acceleration of the photolysis of 2-nitrobenzyl and, consequently, the disruption of the micelles.

PHOTOTHERMAL CONTROLLED RELEASE SYSTEMS

Temperature-induced gel systems with photocontrolled release capability may improve the performance of formulations that can be administered as a free flowing fluid that gels *in situ* due to the temperature change; the viscosity changes under irradiation enable external tuning of drug delivery from the depot. As an example, supramolecular cross-linking of polymers by low-molecular-weight cross-linkers using multiple hydrogen bonds can be used for mediating thermally reversible sol–gel phase transitions (56). The degree of cross-linking of the polymer networks can be controlled though the *trans*-to-*cis* isomerization of azobenzene groups introduced in the cross-linker. Thermally sensitive and photoresponsive supramolecular gels were prepared using poly(trimethylene iminium trifluorosulfonimide) as hydrogen-bond donor and the bifunctional 2,6-bis(benzoxazol-2-yl) pyridine ligand (hydrogen-bond acceptor) with an azobenzene group as cross-linker. The *cis* conformation destabilizes the ladderlike supramolecular assemblies and breaks up the cross-linked aggregates. Therefore, irradiation with UV light (220–410 nm) for 30 min at room temperature led to an increase in the fluidity of the gel. The resulting viscous solution reversibly evolved to a non-flowable gel under visible light (57).

We have developed temperature- and light-responsive systems based on blends of poloxamer 407 (Pluronic® F127) and poly(*N*,*N*-dimethylacrylamide-*co*-methacryloyloxyazobenzene) (DMA–MOAB) copolymer. The DMA–MOAB micelles dissociate into unimers when irradiated with 366 nm light due to the *trans*-to-*cis* isomerization of the azobenzene groups. In the absence of Pluronic, light causes a significant decrease in the viscosity of the medium. By contrast, irradiation of the Pluronic/DMA–MOAB mixed systems results in the entanglement of both copolymers, which enhances the

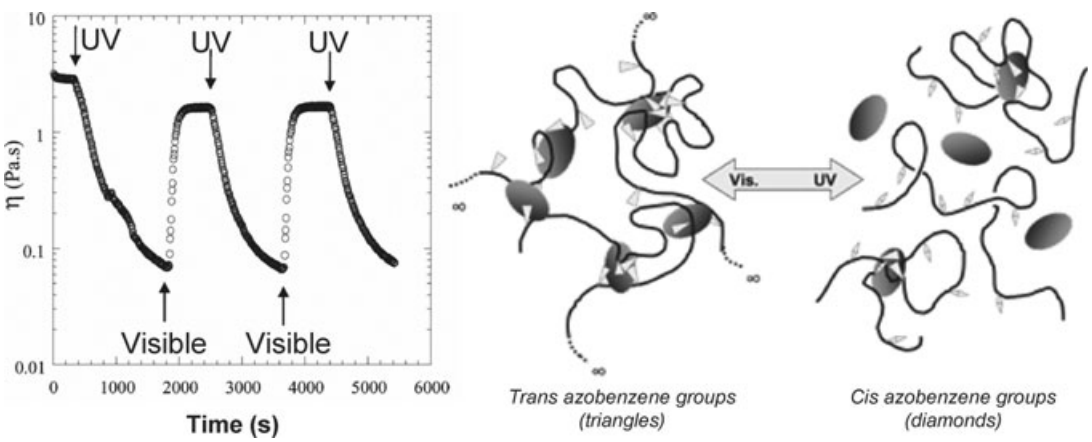

Figure 4. Variation of viscosity of 1 wt% poly(acrylic acid)-1,2-aminoundecilamido-4-phenylazobenzene micellar solution in the presence of bovine seroalbumin under exposure to light, alternating the wavelength between UV (365 nm) and visible (436 nm). Proteins mostly bound under exposure to visible light show significant release under UV exposure. Reproduced from Pouliquen and Tribet (54) by permission of the American Chemical Society.

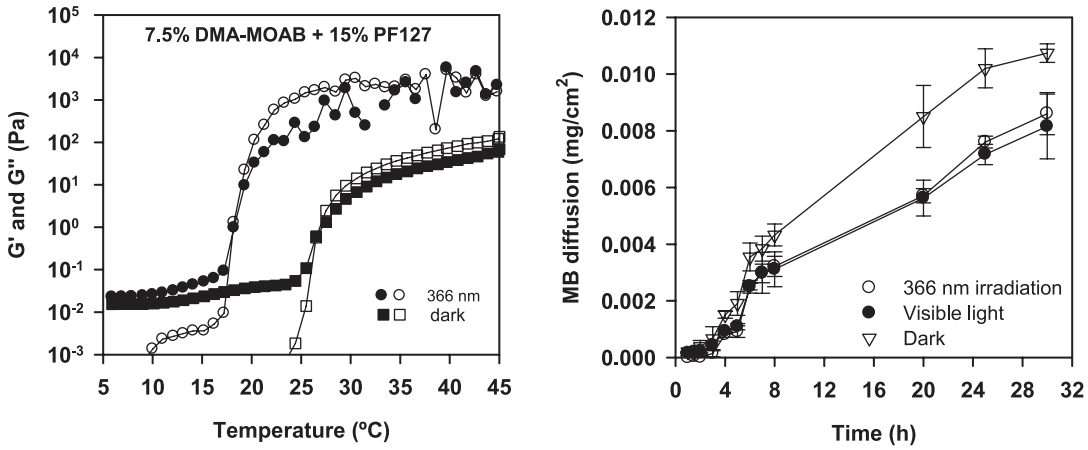

Figure 5. Evolution of the storage (G′, open symbols) and loss (G″, full symbols) moduli of F127:DMA–MOAB 2:1 weight ratio aqueous solutions stored in the dark or after UV irradiation, and methylene blue (MB) diffusion from F127:DMA–MOAB 2:1 weight ratio solutions, through a 0.20 μm pore size membrane under different light conditions. Reproduced from Alvarez-Lorenzo *et al.* (50) by permission of the American Chemical Society.

hydrophobicity of the Pluronic micellar microenvironment and, consequently, triggers the gelation. Under dark conditions, the azobenzene groups of DMA–MOAB in the *trans* conformation self-associate and the interactions with Pluronic are minimal. By contrast, photoconversion to the *cis* frees up the azobenzene groups to interact with the Pluronic micelles. This lowers the gel temperature by 10°C (Fig. 5). If the PF127 concentration is adequately chosen, it is possible to prepare aqueous solutions consisting of PF127:DMA–MOAB 2:1 blends of low viscosity at body temperature under dark conditions, which undergo a sol–gel transition on irradiation with an adequate light source. Such a transition strongly alters the diffusion of the solutes included in the system. This light-induced interaction between the azobenzene moieties of DMA–MOAB and Pluronic micelles disappears when hydroxypropyl-β-cyclodextrin is added to the medium. In the presence of the cyclodextrin the *trans*-to-*cis* isomerization also occurs, but the azobenzene groups in the *cis* conformation form inclusion complexes with the cyclodextrins. As a consequence, the hydrophobic interactions with the Pluronic micelles are prevented and the system loses its photoresponsiveness (50). The light- and temperature-responsiveness of the F127:DMA–MOAB blend solutions prompted a study of the extent to which the conformational changes alter the diffusion of a hydrophilic solute. Methylene blue (MB) is expected to diffuse in the aqueous regions of the polymer matrix, while avoiding the hydrophobic cores. As expected from the aqueous blend gelation seen apparent in its rheological behavior, the MB diffusion rate under dark conditions was significantly faster than when the experiment was carried out at visible light or under 366 nm irradiation (Fig. 5). These results indicate that the *trans*-to-*cis* isomerization enables a control of the rheological and diffusional properties of F127:DMA–MOAB blends for practical purposes such as topical drug delivery.

Another approach for achieving photothermally regulated DDS consists of using dyes or particles capable of absorbing visible or NIR light and efficiently transforming the light energy into local heating. The increase in temperature induces a conformational change (demicellization, volume phase transition) that triggers drug release (58,59). Examples of such systems with light absorbers include polyelectrolyte multilayer shells, which once doped with light-absorbing gold nanoparticles and assembled on the surface of lysozyme crystals, enable a photocontrolled release of the enzyme upon irradiation with short pulses of NIR laser light without causing enzyme damage (60). Similar polyelectrolyte/gold nanoparticle tandem was used to prepare microcapsules that release macromolecules when irradiated at 1064 nm (61). Although the mechanisms involved in the release are not yet clear, the heat generated during irradiation may have caused a significant stress in the capsules, due to different thermal expansion coefficients that ultimately lead to the rupture of the shell. The polyelectrolyte multilayer shell can be modified with lipids and functionalized with specific antibodies for the purposes of enhanced stability and targeted delivery.

Finally, the light-induced heat can be considered as a therapeutic agent in its own right. Nanoparticles with metal shells internalized by tumor tissues can deliver a therapeutic dose of heat by using moderately low exposures of extracorporeally applied NIR light. *In vivo* studies showed that solid tumors treated with metal nanoshells (silica cores surrounded by a gold shell) and exposed to NIR (820 nm) reached temperatures high enough to induce an irreversible tissue damage (62). Compared to the conventional surgical treatments, thermal ablation therapies are less invasive and much simpler, combining a high efficiency with a rapid recovery of the patient. The combination of benign nanoshells and NIR light has a great potential for tailoring therapy regimens to ensure the complete thermal destruction of tumors.

LIGHT-RESPONSIVE LIPOSOMES

Liposomes consist of concentric bilayers of phospholipids and/or other amphiphilic molecules separated by aqueous compartments, resulting in nanosized vesicles. Intensive search has been conducted on liposomes capable of solubilizing and carrying drugs in aqueous fluids, thus prolonging drug circulation in the bloodstream and modulating the drug biodistribution (63,64). Despite improvements in the therapeutic efficacy *versus* side effects obtained with some relevant drugs such as, for instance, amphotericin B and doxorubicin, the desired drug release from liposomes is still a challenge.

Once accumulated in a tissue, the drug is released mainly by passive diffusion. In most cases, this process has been shown to occur too slowly and local drug concentrations required for the optimum therapeutic effect are not reached (40). Therefore, new approaches to trigger a rapid drug release upon the liposome arrival to the desired body site are being investigated (65,66). Destabilization of the liposome structure by an external source of energy is attracting most interest owing to the spatial and temporal control over the drug release that can be exerted. For example, intensive research is being carried out to develop echogenic (*i.e.* sensitive to ultrasonic stimulation) liposomes, which involves the encapsulation of drug with air or gas bubbles (67). Light-responsive liposomes appear to be a feasible alternative. Two reviews about phototriggering drug delivery from liposomes have been published prior to 2001 (40,68). Herein, we will focus on the work published after 2001. The mechanisms involved in creating light-sensitive liposomes have been classified as photopolymerization, photochemical triggering and photoisomerization (40). We will follow this terminology to present the latest achievements in this field. Figure 6 illustrates leading mechanisms of light-triggered drug release from liposomes.

Light-responsiveness based on photopolymerization of membrane lipids

Incorporation of polymerizable compounds with reactive dienoyl, sorbyl or styryl groups into the hydrophobic domains of liposomes causes the bilayers to polymerize and assemble into larger clusters when an adequate source of light is applied. A consequence of the photopolymerization is that temporal pores in the bilayer are formed around the clusters until the surrounding free mobile lipids rearrange to reconstitute the bilayer. Such pores allow drug molecules to diffuse out of the liposome.

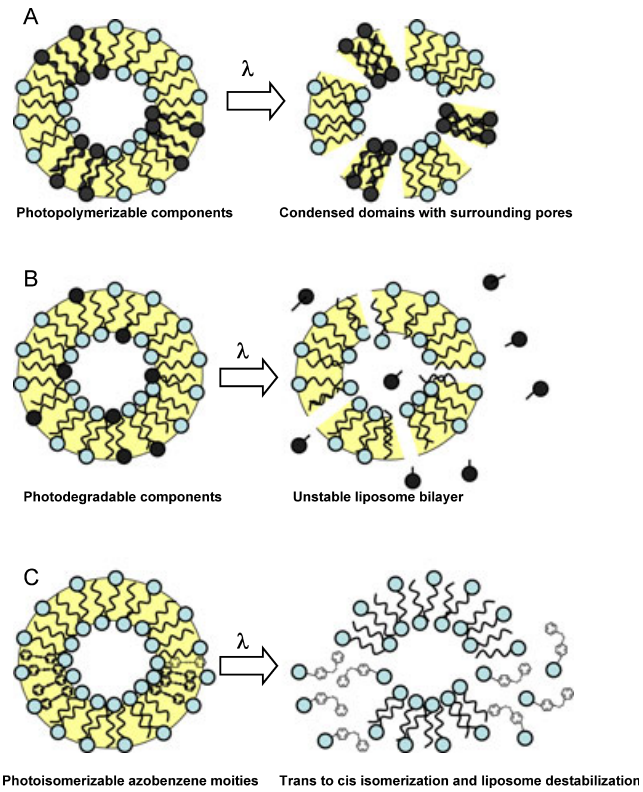

Figure 6. Schematic view of the main mechanisms involved in light-responsive behavior of liposomes.

Stealth liposomes prepared with poly(ethylene glycol) (PEG) are particularly stable in the bloodstream and, consequently, averse to releasing the drug even when the liposome reaches the desired organ. To overcome such a problem, lipids with cross-linkable groups have been incorporated into the liposome structure, with the aim of forming cross-linked domains under UV irradiation that phase-separate from the other lipidic components. The phase separation causes an increase in the permeability of the lamellar structure. For example, the inclusion in PEG-liposomes of the photoreactive lipid 1,2-bis[10-(2′,4′-hexadienoyloxy)decanonyl]-*sn*-glycero-3-phosphocholine (bis-SorbPC$_{17,17}$; Fig. 7) did not alter the permeability of liposomes prior to irradiation (69,70). In contrast, exposure of such liposomes to UV light for 2 min increased the permeability 200-fold. An adequate combination of the photosensitive lipid with the PEG-modified lipid and the saturated phosphatidylcholine enabled the liposomes to have extremely low permeabilities to water-soluble fluorescent probes at 37°C in the dark, yet the permeability increased 28 000-fold upon irradiation at 254 nm. The notable enhancement of the release was attributed to an abrupt phase separation between the photoreactive and saturated phospholipids (see Fig. 6A). During cross-linking, the polymerizable lipids are drawn together resulting in a shrunken domain. It takes some time for the nonpolymerized lipids to fill the vacant area. Consequently, small fissures, through which the drug can migrate out, appear in the liposome bilayer (71).

In addition to the more common liposomes composed of phospholipids, light-sensitive liposomes coated by polymers have been prepared using copolymers with nonpolymerizable (polypropylene) and polymerizable (methacrylate) hydrophobic groups (72). The lipids and the polymer molecules were premixed to allow the hydrophobic blocks of the copolymers to incorporate into the lipid bilayer, resulting in steric stabilization of the vesicles. When UV polymerization of the bilayer was induced, interliposomal fusion was triggered because the polymerized domains induced strain against the high bending curvature of the lipid bilayer. The lateral phase separation at some regions of the bilayer together with the Brownian motion led to the collision between lipid bilayers causing fusion of the liposomes. Such change in the liposome structure is useful in creating a light-triggered DDS. Furthermore, the interliposomal fusion seems to be reversible (72).

Another approach toward liposomes involves associating selected cyanine dyes with the lipid bilayer (73). For example, a cationic dye, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) or corresponding anionic

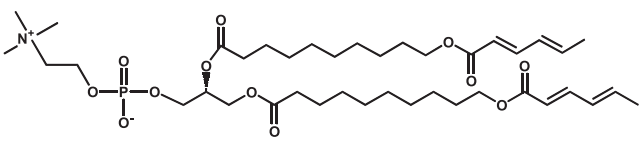

Figure 7. Photoreactive lipid 1,2-bis[10-(2′,4′-hexadienoyloxy)decanonyl]-*sn*-glycero-3-phosphocholine (bis-SorbPC$_{17,17}$).

disulfonated DiI (DiI-DS) included in the membrane of large (100 nm) unilamellar liposomes made of DOPE and bis-SorbPC (molar ratio 3:1) triggered the bilayer rupture and delivery of the liposomal content when irradiated at 550 nm. The light at this wavelength is only absorbed by the DiI dye and not by the lipids. The liposomes also showed pH-dependent delivery. The photoinduced release was much faster at pH 4.5 than at higher pH. Experiments with HeLa cells demonstrated that the photosensitive liposomes were efficiently incorporated into the cells by endocytosis and remained in the endosome without releasing the drug when the cells were kept in the dark. Irradiation at 550 nm induces liposome destabilization. Membrane rupture results in drug leakage from the liposome interior and the fusion of the liposomes with the endosome membrane. This leads to the delivery of the liposomal content to the cytoplasm of the cell. Such an approach may be useful in creating liposomes that can escape the endosomal or lisosomal vacuoles and make the intact drug available for interaction with the target intracellular organelles (73).

Liposome responsive to light on the basis of photochemical triggering

Various chemical mechanisms can cause the rupture of the assembly of the liposomal lipidic components, leading to bilayer destabilization and the release of the liposomal content (see Fig. 6B). These mechanisms are as follows.

Photooxidation. Liposomes containing plasmenylcholine undergo a lamellar to hexagonal phase change when the constitutive lipids are cleaved to single-chain surfactants using a 630–820 nm light (Fig. 8) (74). Singlet oxygen, formed by irradiation of a suitable sensitizer in the presence of oxygen, leads to the photooxidation of the plasmalogen vinyl ether linkage. Plasmenylcholine is then decomposed to fatty aldehydes and lysolipids, inducing the phase transition and thus promoting membrane fusion and the leakage of the intraliposomal content (40,68). The nature and concentration of the membrane sensitizer determine the rate of the photoinitiated release. For example, the use of the NIR sensitizer bacteriochlorophyll *a* led to 100% calcein release in less than 20 min when irradiated at 800 nm. The observed release rate was 2 orders of magnitude faster than from the control egg lecithin liposomes prepared without the sensitizer and irradiated under identical experimental conditions (74). The penetration depth over 1 cm of the light at this wavelength and the possibility of combining phototriggering and photodynamic therapy (including the photodynamic sensitizer in the liposome membrane) makes this approach particularly promising (40).

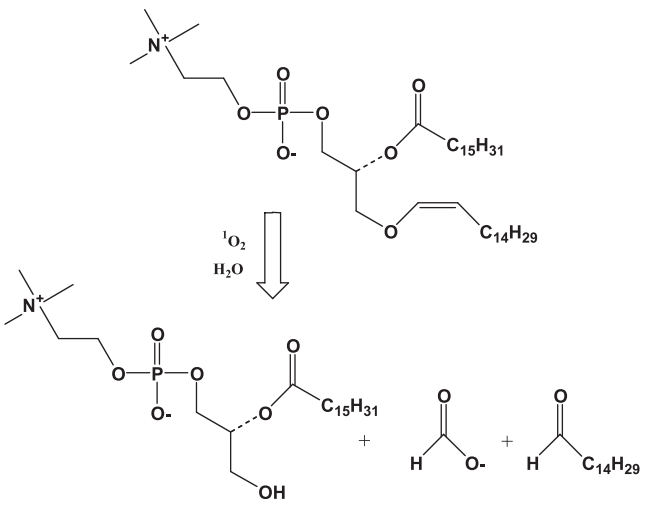

Figure 8. Singlet oxygen-mediated photooxidation of plasmenylcholine leading to the rupture of the plasmalogen vinyl ether linkage, which degrades with UV light and does not polymerize.

Liposomes containing plasmenylcholine and calcium ions are being explored to induce Ca^{2+}-mediated processes. Successful *in vitro* results have been obtained for the activation of enzymatic reactions (75) and inducing the *in situ* gelation of peptide or polymer solutions (76). Aqueous human fibrinogen and transglutaminase (TGase) solution containing liposomes composed of 38:57:5 diplasmenylcholine (DPPlsC):distearoylphosphatidylcholine (DSPC):bacteriochlorophyll (Bchl) with entrapped $CaCl_2$ remained fluid for several hours in the dark. Exposure of the system to 800 nm irradiation resulted in gelation due to the photosensitized Ca^{2+} release and the TG-induced fibrinogen cross-linking (Fig. 9) (77). This approach to the phototriggered formation of hydrogels creates new opportunities for biomaterial applications in drug delivery, tissue engineering and wound healing.

Photodeprotection of fusogenic lipids. Certain photocleavable lipids can lead to stable liposomes that rapidly destabilize when irradiation causes the hydrolysis of the lipid (78). Several derivatives are being evaluated for such a purpose. For example, a photocleavable derivative of 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) termed NVOC-DOPE decomposes to 3,4-dimethoxy-2-nitrosobenzaldehyde and DOPE when irradiated with a Xe source lamp ($\lambda >$ 300 nm). If incorporated to liposomes, 20 min of irradiation induces the release of up to 50% of the liposome contents (calcein) within 40 min (Fig. 10) (78).

Amphiphilic lipids prepared from stearyl amine (serving as a nonpolar tail) conjugated to charged amino acids (polar heads of the resulting lipid) *via* the *o*-nitrobenzyl derivatives undergo photocleavage reaction by UV light ($\lambda >$ 320 nm) (79). The rate of the cleavage reaction depended strongly on the nature of the amino acid. Aspartic and glutamic acids containing lipids were found to break more easily than a lysine-containing lipid. This is because the side chain groups of the amino acids influence the electronic structure of the lipid and the nature of the intermediate species during degradation. Liposomes prepared using any of these lipids showed a two-step phototriggered release of an encapsulated dye, with varying rates (79). The first step in the release is the photocleavage of lipids, the rate of which depends on whether the amino acid is acidic or basic in nature. The second, slower step refers to the release of the liposomal content, which is dictated by the organization of the lipid domains following the separation of the amino acid head groups (Fig. 11).

Light-responsiveness based on photopolymerization of membrane lipids and on photochemical triggering considered above involves irreversible processes. This means that the liposomes based in these mechanisms are of a single use, *i.e.* once the delivery is triggered it cannot be stopped and the liposome disintegrates. Thus, although stimuli sensitive, these

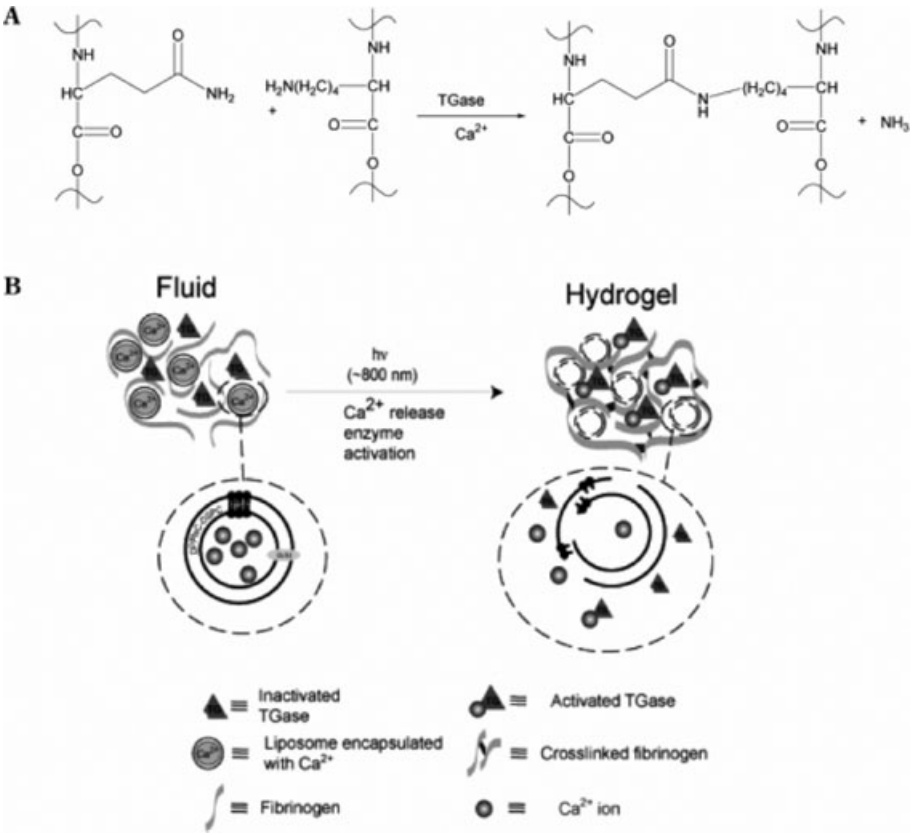

Figure 9. Glutamine-lysine cross-linking reaction catalyzed by calcium-dependent transglutaminase (TGase) (A) and conceptual illustration of the photoinduced fibrinogen gelation process (B). Reproduced from Zhang *et al.* (77) by permission of the American Chemical Society.

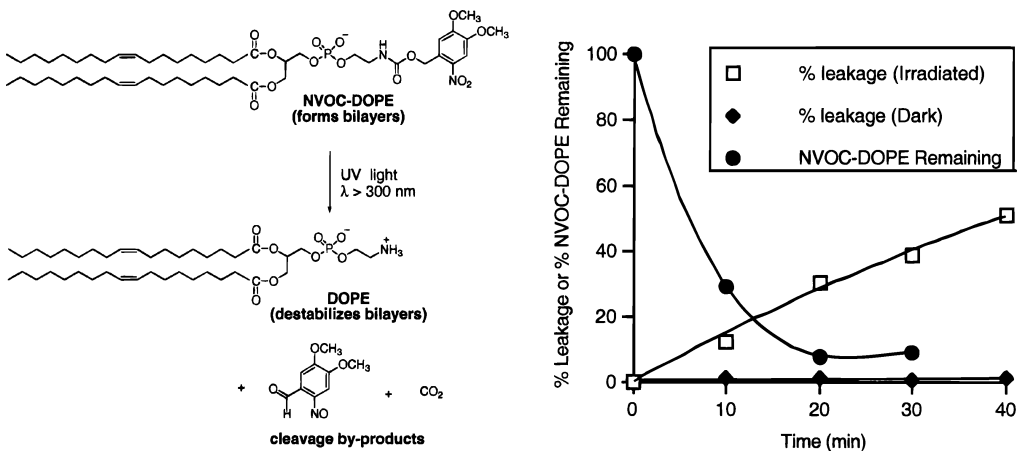

Figure 10. Mechanism of NVOC-DOPE photocleavage and calcein release from 1:1 EPE/NVOC-DOPE liposomes at pH 5 and 37°C, upon irradiation with 150 W lamp. Reproduced from Zhang and Smith (78) by permission of the American Chemical Society.

liposomes cannot be considered truly "intelligent," a term that is usually reserved to systems able to undergo reversible activation/deactivation when the triggering agent appears/disappears. The next section deals with intelligent liposomes capable of showing switchable delivery of their content by light, *i.e.* they can deliver the hosted drug in a pulsatile manner. Each time the stimulus is applied, a certain drug dose is released. The entire dose is administered after multiple pulses (multipulsatile DDS).

Light-responsive liposomes based on photoisomerizable lipids

Lipids containing azobenzene groups such as dipalmitoylphosphatidylcholine with acyl chains bearing azobenzene moieties (Bis-Azo PC) can undergo photoisomerization that leads to photoinduced conformational changes in the liposomes. The *trans*-to-*cis* isomerization of the azobenzene groups alters the polarity and conformation of the lipids in a rapid and reversible fashion (Fig. 12) (32,80). As discussed

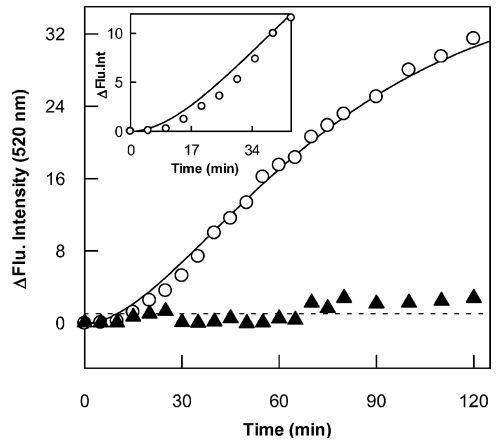

Figure 11. Kinetic profiles for the release of carboxyfluorescein upon irradiation of liposomes containing lysine-lipid. The increase in the dye fluorescence intensity (ΔF_{518}/nm; λ_{exc} = 495 nm) as a function of time upon irradiation of liposomes (open circles) and when they are kept in the dark (control experiment; filled triangles) are shown. The inset shows an expansion of the data at the initial time scale to show the initial lag phase. Reproduced from Chandra *et al.* (79) by permission of The Royal Society of Chemistry.

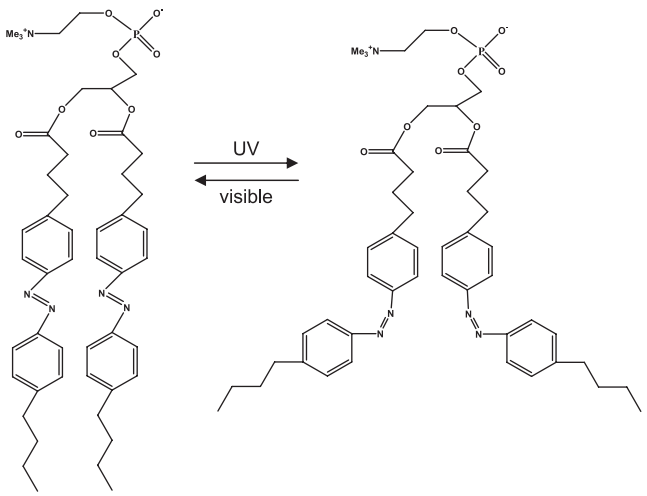

Figure 12. Structure of the photochromic lipid Bis-Azo PC.

previously, aggregates comprising azobenzene moieties in their *trans* form are more stable thermodynamically than in the *cis* form. The *trans* form enables a more compact packing of the hydrophobic chains in the liposome bilayer. Liposomes containing 6% mol/mol of Bis-Azo PC are stable in the dark and retain trapped solutes for months at room temperature. UV-light irradiation causes the photoisomerization to the less stable *cis* form and accelerates the release of the entrapped solutes. The *cis*-to-*trans* isomerization reverses under visible light irradiation. A fine control of drug release can be achieved by adjusting the liposome composition. For example, an increase in cholesterol content reduces the extent of photoisomerization necessary for the release to occur, increasing the light sensitivity of azobenzene-containing liposomes (32). Thus, an adequate combination of liposomes prepared with and without cholesterol enables a simultaneous control of the delivery of two drugs triggered by light at two different wavelengths. This approach has been tested *in vitro* for the delivery of calcein activated at 470 nm and of sulforhodamine-B activated at 355 nm from a mixture of liposomes with and without cholesterol, respectively.

To prevent premature liposome destabilization and to improve the performance as multipulsatile DDS, Liu *et al.* (81) prepared cholesterol derivatives containing Bis-Azo PC and different polar groups. Small unilamellar liposomes were prepared with amphiphilic cholesterol derivatives, phosphatidylcholine and calcein, and their behavior evaluated both in the gel state (15°C) and the liquid crystal state (37°C). The liposome dispersion was irradiated every 4 h with UV light (for 10 min) or visible light (15 min). Irradiation with UV light greatly enhanced the release rate of calcein whereas visible light irradiation completely stopped the release. The on–off switching was more pronounced at 37 than at 15°C owing to the temperature dependence of the drug diffusion. Nevertheless, photoisomerization did not compromise liposome integrity, either in the gel state or in the liquid crystal state, and thus a pulsatile delivery could be achieved.

LIGHT-RESPONSIVE NANOCOMPOSITES

An interest in combining light-sensitive polymers and inorganic substrates in a single system has been recently highlighted that can help achieve improved mechanical properties and control of the loading and release of guest substances (82–84). Silica nanoparticles are biocompatible and readily modifiable with new functionalities useful for application in drug delivery devices (85). Light-responsive silica nanoparticles (70 nm) were prepared by covalent conjugation of photoactive *o*-nitrobenzyl bromide molecules with amino groups on the particle surface (86). Drugs with carboxylic, phosphate or hydroxy groups were covalently attached to the *o*-nitrobenzyl bromide groups. When the resulting particles are irradiated at 310 nm, the *o*-nitrobenzyl bromide groups transform into o-nitrobenzaldehyde, which causes an irreversible cleavage of the drug–particle bond, leading to drug release. These particles are small enough to penetrate into cells, enabling an external control of the intracellular drug release.

Another approach toward a nanocomposite-based DDS is to use azobenzene chains as both impellers and nanovalves when they are tethered within and onto mesoporous silica nanoparticles (Fig. 13). The pores in silica materials can be designed using templating agents such as surfactants that are removed when the structure is complete. To control solute diffusion within the pores, the pore walls can be derivatized with molecules acting as nanovalves by reversibly changing their conformation. Derivatization of the pores with azobenzene chains is of interest because of the reversibility of azobenzene isomerization. Within the framework of this concept, zeolite membranes modified with azobenzene were shown to possess photoswitchable gas permeation properties regulated by the *trans*-to-*cis* isomerization of the azobenzene moieties (87). Similarly, azobenzene-modified cubic-structured silica films enabled the control of the transport of ferrocene derivatives to an electrode surface (88). Angelos *et al.* (89) explored the possibility of a continuous excitation of spherical silica nanoparticles with a small azobenzene derivative (AzoH) attached to the pore interiors at 457 nm, and a larger azobenzene derivative (AzoG1) attached to the pore openings

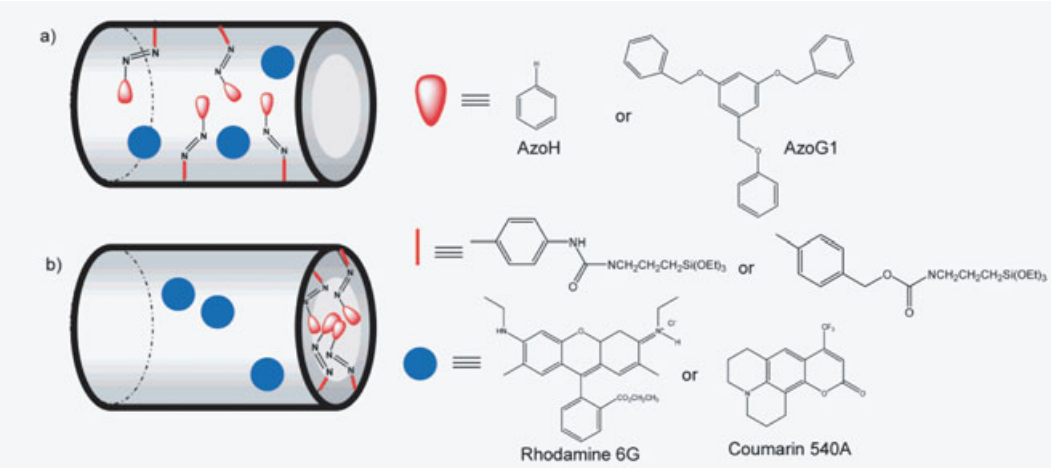

Figure 13. Photoresponsive materials based on silica particles functionalized with azobenzene derivatives for creating impellers (a; attaching small azobenzene derivatives AzoH to the pore interiors) or nanovalves (b; attaching large azobenzene derivatives AzoG1 to the pore openings). For each system, the moveable phenyl ring of the azobenzene machine is illustrated by the red inverse teardrop, the tethered phenyl ring of the azobenzene machine by the red vertical bar and the impelled molecule by the blue circle. Reproduced from Angelos *et al*. (89) by permission of the American Chemical Society.

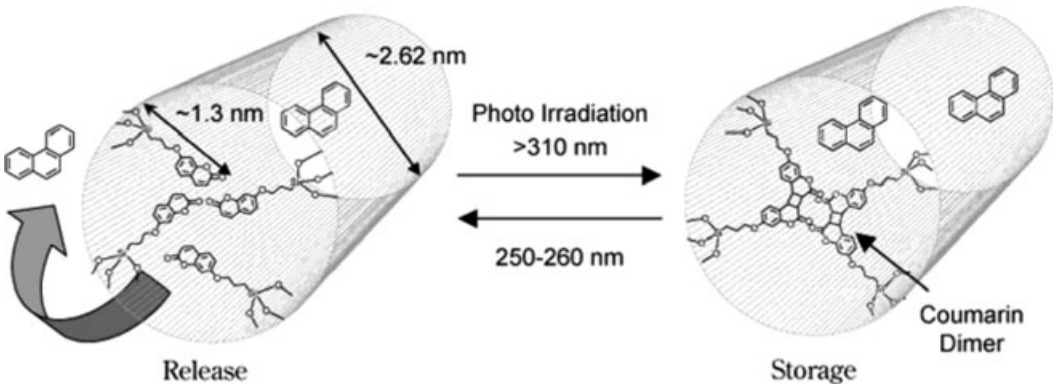

Figure 14. Schematic view of photoswitched storage-release controlled release by coumarin-modified silica MCM-41 particles. Reproduced from Mal *et al*. (35) by permission of the American Chemical Society.

(Fig. 13). Both the *cis* and *trans* derivative conformers absorb light at 457 nm, which causes isomerization and results in a dynamic wagging of the moving parts of the azobenzene derivative. Prior to the excitation, the guest molecules (rhodamine 6G and coumarin 540A) hosted in the pores cannot diffuse out because of the high density of the azobenzene chains. Excitation caused azobenzene chains to wag in predominant directions, opening diffusion pathways and expelling the guest molecules out of the pores. The concentration of azobenzene chains determines the diffusitivity inside the pores and enables the on–off switching of the solute transport.

Further advances along this research line enabled the preparation of nanoimpeller-controlled mesostructured silica nanoparticles to deliver and release anticancer drugs into living cells on demand (90). Experiments carried out with human cancer cell lines showed that once the nanoparticles were taken up by the cells, the anticancer drug camptothecin was only released inside of cells that were illuminated at 413 nm to activate the impellers. The nanoimpellers are azobenzene moieties positioned in the pore interiors with one end attached to the walls and the other end free to undergo photoisomerization. As *cis* and *trans* azobenzene isomers have almost the same extinction coefficient at 413 nm, irradiation at this wavelength causes the azobenzene moieties to move back and forward, driving the drug molecules out of the silica pores. Applying this mechanism, we envision that intracellular release and, consequently, cell apoptosis can be controlled by light intensity, irradiation time and wavelength.

The intermolecular reversible photodimerization and photocleavage of coumarin derivatives has also been tested for regulating the passage of guest molecules through the narrow pores (*ca* 2–4 nm diameter) of silica particles. A photoresponsive coumarin derivative was grafted on the pore outlet of particles acting as an "open-close double doors" system. Irradiation with UV light longer than 310 nm wavelength induced the photodimerization of coumarin to close the pore outlet with cyclobutane dimer (Fig. 14). Guest molecules such as phenanthrene neither can enter nor escape from the individual pores of the particles. On the other hand, irradiation with shorter wavelength UV light (~250 nm) regenerates the coumarin monomer, the pores are opened and the guest molecules can be released (35).

CURRENT AND FUTURE DEVELOPMENTS

Light-sensitiveness is a quite attractive phenomenon for developing advanced DDS capable of a precise external modulation of the site and the rate of delivery. A wide range of approaches is currently under study to optimize the light-responsive materials in order to achieve therapeutically efficient and reproducible release profiles. Nevertheless, the clinical use of the light-sensitive DDS still requires considerable additional efforts, especially regarding the following aspects:

(1) Design and synthesis of new biocompatible materials in order to increase the range of light-sensitive lipids and polymers that fulfill the requirements of generally recognized safe products. Azobenzene groups and the like that are perceived to be toxic by the FDA limit the application of such DDS to topical formulations.
(2) Specialized equipment capable of providing the adequate irradiation intensity in the target place without altering surrounding tissues. The relative impermeability of the human body to the light makes a direct irradiation at a significant depth of the body difficult and confines the applicability of the UV/visible light-sensitive DDS to treatments of the surface layers of the skin or a few millimeters beyond. NIR lasers and NIR-sensitive light materials appear to be feasible alternatives to their UV/visible counterparts.
(3) *In vivo* evaluation of the performance of new delivery systems. Currently, most of the reviewed systems were only tested *in vitro*. These studies must be supplemented by studies *in vivo* as the DDS make progress toward clinical use.

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REFERENCES

1. Vauthier, C. and D. Labarre (2008) Modular biomimetic drug delivery systems. *J. Drug Del. Sci. Tech.* **18**, 59–68.
2. Bayer, C. L. and N. A. Peppas (2008) Advances in recognitive, conductive and responsive delivery systems. *J. Control. Release* **132**, 216–221.
3. Youan, B. B. C. (2004) Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery? *J. Control. Release* **98**, 337–353.
4. Alvarez-Lorenzo, C. and A. Concheiro (2008) Intelligent drug delivery systems: Polymeric micelles and hydrogels. *Mini Rev. Med. Chem.* **8**, 1065–1074.
5. Anil, A. K. (2007) Stimuli-induced pulsatile or triggered release delivery systems for bioactive compounds. *Recent Pat. Endocr. Metab. Immune Drug Discovery* **1**, 83–90.
6. Kost, J. and R. Langer (2001) Responsive polymeric delivery systems. *Adv. Drug Deliv. Rev.* **46**, 125–148.
7. Sershen, S. and J. West (2002) Implantable, polymeric systems for modulated drug delivery. *Adv. Drug Deliv. Rev.* **54**, 1225–1235.
8. Qiu, Y. and K. Park (2001) Environment-sensitive hydrogels for drug delivery. *Adv. Drug Deliv. Rev.* **53**, 321–339.
9. Murdan, S. (2003) Electro-responsive drug delivery from hydrogels. *J. Control. Release* **92**, 1–17.
10. Sunil, A., R. V. Kulkarni, N. N. Mallikarjuna, P. V. Kulkarni and T. M. Aminabhavi (2005) Electrically modulated transport of diclofenac salts through hydrogels of sodium alginate, carbopol, and their blend polymers. *J. Appl. Polym. Sci.* **96**, 301–311.
11. Rapoport, N. (2007) Physical stimuli-responsive polymeric micelles for anti-cancer drug delivery. *Prog. Polym. Sci.* **32**, 962–990.
12. Andresen, T. L., S. S. Jensen and K. Jorgensen (2005) Advanced strategies in liposomal cancer therapy: Problems and prospects of active and tumor specific drug release. *Prog. Lipid Res.* **44**, 68–97.
13. Barrett, C. and O. Mermut (2005) Polymer multilayer films with azobenzene for photoactive biosurfaces. *PMSE Preprints* **92**, 51–52.
14. Chung, C. M., Y. S. Roh, S. Y. Cho and J. G. Kim (2004) Crack healing in polymeric materials via photochemical [2 + 2] cycloaddition. *Chem. Mater.* **16**, 3982–3984.
15. Wu, D. Y., S. Meure and D. Solomon (2008) Self-healing polymeric materials: A review of recent developments. *Prog. Polym. Sci.* **33**, 479–522.
16. Jiang, H., S. Kelch and A. Lendlein (2006) Polymers move in response to light. *Adv. Mater.* **18**, 1471–1475.
17. Lendlein, A., H. Jiang, O. Jünger and R. Langer (2005) Light-induced shape-memory polymers. *Nature* **434**, 879–882.
18. Rosario, R., D. Gust, M. Hayes, F. Jahnke, J. Springer and A. A. Garcia (2002) Photon-modulated wettability changes on spiropyran-coated surfaces. *Langmuir* **18**, 8062–8069.
19. Kameda, M., K. Sumaru, T. Kanamori and T. Shinbo (2003) Photoresponse gas permeability of azobenzene-functionalized glassy polymer films. *J. Appl. Polym. Sci.* **88**, 2068–2072.
20. Sumaru, K., K. Ohi, T. Takagi, T. Kanamori and T. Shinbo (2006) Photoresponsive properties of poly(n-isopropylacrylamide) hydrogel partly modified with spirobenzopyran. *Langmuir* **22**, 4353–4356.
21. Garcia, A., M. Marquez, T. Cai, R. Rosario, Z. Hu, D. Gust, M. Hayes, S. A. Vail and C. D. Park (2007) Photoresponsive properties of poly(n-isopropylacrylamide) hydrogel partly modified with spirobenzopyran. *Langmuir* **23**, 224–229.
22. Lohmann, D. and K. Petrak (1989) Photoactivation and photocontrolled release of bioactive materials. *Crit. Rev. Ther. Drug Carrier Syst.* **5**, 263–320.
23. Jiang, J., X. Tong, D. Morris and Y. Zhao (2006) Toward photocontrolled release using light-dissociable block copolymer micelles. *Macromolecules* **39**, 4633–4640.
24. Normand, N., F. Valamanesh, M. Savoldelli, F. Mascarelli, D. BenEzra, Y. Courtois and F. Behar-Cohen (2005) VP22 light controlled delivery of oligonucleotides to ocular cells in vitro and in vivo. *Mol. Vis.* **11**, 184–191.
25. Donnelly, R. F., P. Juzenas, P. A. McCarron, A. D. Woolfson and J. Moan (2006) Drug delivery for topical photodynamic therapy: Difficulties and novel solutions. *Trends Cancer Res.* **2**, 1–20.
26. McCoy, C. P., C. Rooney, C. R. Edwards, D. S. Jones and S. P. Gorman (2007) Light-triggered molecule-scale drug dosing devices. *J. Am. Chem. Soc.* **129**, 9572–9573.
27. Juzenas, P., A. Juzeniene, O. Kaalhus, V. Iani and J. Moana (2002) Noninvasive fluorescence excitation spectroscopy during application of 5-aminolevulinic acid in vivo. *Photochem. Photobiol. Sci.* **1**, 745–748.
28. Klohs, J., A. Wunder and K. Licha (2008) Near-infrared fluorescent probes for imaging vascular pathophysiology. *Basic Res. Cardiol.* **103**, 144–151.
29. Weissleder, R. and V. Ntziachristos (2003) Shedding light onto live molecular targets. *Nat. Med.* **9**, 123–128.
30. Mochizuki-Oda, N., Y. Kataoka, Y. Cui, H. Yamada, M. Heya and K. Awazu (2002) Effects of near-infrared laser irradiation on adenosine triphosphate and adenosine diphosphate contents of rat brain tissue. *Neurosci. Lett.* **323**, 207–210.
31. Nagasaki, T. and S. Shinkai (2007) The concept of molecular machinery is useful for design of stimuli-responsive gene delivery systems in the mammalian cell. *J. Incl. Phenom. Macro.* **58**, 205–219.
32. Bisby, R. H., C. Mead and C. G. Morgan (2000) Wavelength-programmed solute release from photosensitive liposomes. *Biochem. Biophys. Res. Commun.* **276**, 169–173.
33. Wilson, B. C. and M. S. Patterson (2008) The physics, biophysics and technology of photodynamic therapy. *Phys. Med. Biol.* **53**, R61–R109.
34. Al-Tahami, K. and J. Singh (2007) Smart polymer based delivery systems for peptides and proteins. *Recent Pat. Drug Delivery Formulation* **1**, 65–71.

35. Mal, N. K., M. Fujiwara, Y. Tanaka, T. Taguchi and M. Matsukata (2003) Photo-switched storage and release of guest molecules in the pore void of coumarin-modified MCM-41. *Chem. Mater*. **15**, 3385–3394.
36. Szczubialka, K. and M. Nowakowska (2003) Response of micelles formed by smart terpolymers to stimuli studied by dynamic light scattering. *Polymer* **44**, 5269–5274.
37. Eastoe, J., A. Vesperinas, A. C. Donnewirth, P. Wyatt, I. Grillo, R. K. Heenan and S. Davis (2006) Photodestructible vesicles. *Langmuir* **22**, 851–853.
38. Levrand, B. and A. Herrmann (2006) Light-induced controlled release of fragrance aldehydes from 1-alkoxy-9,10-anthraquinones for applications in functional perfumery. *Flavour Frag. J*. **21**, 400–409.
39. Zhao, Y. (2007) Rational design of light-controllable polymer micelles. *Chem. Rec*. **7**, 286–294.
40. Shum, P., J. M. Kim and D. H. Thompson (2001) Phototriggering of liposomal drug delivery systems. *Adv. Drug Deliv. Rev*. **53**, 273–284.
41. Wang, G., X. Tong and Y. Zhao (2004) Preparation of azobenzene-containing amphiphilic diblock copolymers for light-responsive micellar aggregates. *Macromolecules* **37**, 8911–8917.
42. Tian, F., Y. Yu, C. Wang and S. Yang (2008) Consecutive morphological transitions in nanoaggregates assembled from amphiphilic random copolymer via water-driven micellization and light-triggered dissociation. *Macromolecules* **41**, 3385–3388.
43. Rijcken, C. J. F., O. Soga, W. E. Hennink and C. F. van Nostrum (2007) Triggered destabilisation of polymeric micelles and vesicles by changing polymers polarity: An attractive tool for drug delivery. *J. Control. Release* **120**, 131–148.
44. Hayashita, T., T. Kurosawas, T. Miyata, K. Tanaka and M. Igawa (1994) Effect of structural variation within cationic azo-surfactant upon photoresponsive function in aqueous-solution. *Colloid Polym. Sci*. **272**, 1611.
45. Shin, J. Y. and N. L. Abbott (1999) Using light to control dynamic surface tensions of aqueous solutions of water soluble surfactants. *Langmuir* **15**, 4404–4410.
46. Eastoe, J., M. Sanchez-Dominguez, P. Wyatt, A. Beeby and R. K. Heenan (2002) Properties of a stilbene-containing gemini photosurfactant: Light-triggered changes in surface tension and aggregation. *Langmuir* **18**, 7837–7844.
47. Eastoe, J., M. Sanchez-Dominguez, H. Cumber, G. Burnett, P. Wyatt and R. K. Heenan (2003) Photoresponsive micro-emulsions. *Langmuir* **19**, 6579–6581.
48. Shang, T., K. A. Smith and T. A. Hatton (2003) Photoresponsive surfactants exhibiting unusually large, reversible surface tension changes under varying illumination conditions. *Langmuir* **19**, 10764–10773.
49. Lee, C. T., K. A. Smith and T. A. Hatton (2004) Photoreversible viscosity changes and gelation in mixtures of hydrophobically modified polyelectrolytes and photosensitive surfactants. *Macromolecules* **37**, 5397–5405.
50. Alvarez-Lorenzo, C., S. Deshmukh, L. Bromberg, T. A. Hatton, I. Sandez-Macho and A. Concheiro (2007) Temperature- and light-responsive blends of pluronic f127 and poly(*n,n*-dimethylacrylamide-co-methacryloyloxyazobenzene). *Langmuir* **23**, 11475–11481.
51. El Halabieh, R. H., O. Mermut and C. J. Barrett (2004) Using light to control physical properties of polymers and surfaces with azobenzene chromophores. *Pure Appl. Chem*. **76**, 1445–1465.
52. Tong, X., G. Wang, A. Soldera and Y. Zhao (2005) How can azobenzene block copolymer vesicles be dissociated and reformed by light? *J. Phys. Chem. B* **109**, 20281–20287.
53. Deshmukh, S., L. Bromberg, K. A. Smith and T. A. Hatton (2006) Photoresponsive, amphiphilic copolymers of azobenzene and *N*, *N*-dimethylacrylamide. *PMSE Preprints* **95**, 878–880.
54. Pouliquen, G. and C. Tribet (2006) Light-triggered association of bovine serum albumin and azobenzene-modified poly(acrylic acid) in dilute and semidilute solutions. *Macromolecules* **39**, 373–383.
55. Jiang, J., X. Tong and Y. Zhao (2005) A new design for light-breakable polymer micelles. *J. Am. Chem. Soc*. **127**, 8290–8291.
56. Hirst, A. R. and D. K. Smith (2005) Two-component gel-phase materials. Highly tunable self-assembling systems. *Chem. Eur. J*. **11**, 5496–5508.
57. Suzuki, T., S. Shinkai and K. Sada (2006) Supramolecular cross-linked linear poly(trimethylene iminium trifluorosulfonimide) polymer gels sensitive to light and thermal stimuli. *Adv. Mater*. **18**, 1043–1046.
58. Sershen, S. R., S. L. Westcott, N. J. Hallas and J. L. West (2000) Temperature-sensitive polymer nanoshell composites for photothermally modulated drug delivery. *J. Biomed. Mater. Res*. **51**, 293–298.
59. Gorelikov, I., L. M. Field and E. Kumacheva (2004) Hybrid microgels photoresponsive in the near-infrared spectral range. *J. Am. Chem. Soc*. **126**, 15938–15939.
60. Radt, B., T. A. Smith and F. Caruso (2004) Optically addressable nanostructured capsules. *Adv. Mater*. **16**, 2184–2189.
61. Angelatos, A. S., B. Radt and F. Caruso (2005) Light-responsive polyelectrolyte/gold nanoparticle microcapsules. *J. Phys. Chem. B* **109**, 3071–3076.
62. Hirsch, L. R., R. J. Stafford, J. A. Bankson, S. R. Sershen, B. Rivera, R. E. Price, J. D. Hazle, N. J. Halas and J. L. West (2003) Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc. Natl Acad. Sci. USA* **100**, 13549–13554.
63. Bonacucina, G., M. Cespi, M. Misici-Falzi and G. F. Palmieri (2009) Colloidal soft matter as drug delivery system. *J. Pharm. Sci*. **98**, 1–42.
64. Immordino, M. L., F. Dosio and L. Cattel (2006) Stealth liposomes: Review of the basic science, rationale, and clinical applications, existing and potential. *Int. J. Nanomedicine* **1**, 297–315.
65. Kim, J. D., S. Y. Bae, J. C. Kim and E. O. Lee (2003) Surface modifications of liposomes for recognition and response to environmental stimuli. In *Adsorption and Aggregation of Surfactants in Solution* (Edited by K. L. Mittal and D. O. Shah), pp. 555–577. Marcel Dekker, New York.
66. Kono, K. (2006) Stimuli responsive polymer-liposomes. Formulation and in vitro evaluation. In *Smart Nano and Microparticles* (Edited by K. Kono and R. Arshady), pp. 91–123. Kentus Books, London.
67. Huang, S. L. (2008) Liposomes in ultrasonic drug and gene delivery. *Adv. Drug Deliv. Rev*. **60**, 1167–1176.
68. Gerasimov, O. V., J. A. Boomer, M. M. Qualls and D. H. Thompson (1999) Cytosolic drug delivery using pH- and light-sensitive liposomes. *Adv. Drug Deliv. Rev*. **38**, 317–338.
69. Gerasimov, O. V., Y. Rui and D. H. Thompson (1996) Triggered release from liposomes mediated by physically- and chemically-induced phase transitions. In *Vesicles* (Edited by M. Rosoff), pp. 679–746. Marcel Dekker, New York.
70. Bondurant, B., A. Mueller and D. F. O'Brien (2001) Photoinitiated destabilization of sterically stabilized liposomes. *Biochim. Biophys. Acta* **1511**, 113–122.
71. Spratt, T., B. Bondurant and D. F. O'Brien (2003) Rapid release of liposomal contents upon photoinitiated destabilization with UV exposure. *Biochim. Biophys. Acta* **1611**, 35–43.
72. Kostarelos, K., D. Emfietzoglou and T. F. Tadros (2005) Light-sensitive fusion between polymer-coated liposomes following physical anchoring of polymerisable polymers onto lipid bilayers by self-assembly. *Faraday Discuss*. **128**, 379–388.
73. Miller, C. R., P. J. Clapp and D. F. O'Brien (2000) Visible light-induced destabilization of endocytosed liposomes. *FEBS Lett*. **467**, 52–56.
74. Thompson, D. H., O. V. Gerasimov, J. J. Wheeler, Y. J. Rui and V. C. Anderson (1996) Triggerable plasmalogen liposomes: Improvement of system efficiency. *Biochim. Biophys. Acta* **1279**, 25–34.
75. Wymer, N. J., O. V. Gerasimov and D. H. Thompson (1998) Cascade liposomal triggering: Light-induced Ca^{2+} release from diplasmenylcholine liposomes triggers PLA(2)-catalyzed hydrolysis and contents leakage from DPPC liposomes. *Bioconjug. Chem*. **9**, 305–308.
76. Collier, J. H., B. H. Hu, J. W. Ruberti, J. Zhang, P. Shum, D. H. Thompson and P. B. Messersmith (2001) Thermally and photochemically triggered self-assembly of peptide hydrogels. *J. Am. Chem. Soc*. **123**, 9463–9464.
77. Zhang, Z. Y., P. Shum, M. Yates, P. B. Messersmith and D. H. Thompson (2002) Formation of fibrinogen-based hydrogels using

phototriggerable diplasmalogen liposomes. *Bioconjug. Chem.* **13**, 640–646.
78. Zhang, Z. Y. and B. D. Smith (1999) Synthesis and characterization of NVOC-DOPE, a caged photoactivatable derivative of dioleoylphosphatidylethanolamine. *Bioconjug. Chem.* **10**, 1150–1152.
79. Chandra, B., R. Subramaniam, S. Mallik and D. K. Srivastava (2006) Formulation of photocleavable liposomes and the mechanism of their content release. *Org. Biomol. Chem.* **4**, 1730–1740.
80. Yagai, S., T. Karatsu and A. Kitamura (2005) Photocontrollable self-assembly. *Chem. Eur. J.* **11**, 4054–4063.
81. Liu, X. M., B. Yang, Y. L. Wang and J. Y. Wang (2005) Photoisomerisable cholesterol derivatives as photo-trigger of liposomes: Effect of lipid polarity, temperature, incorporation ratio, and cholesterol. *Biochim. Biophys. Acta* **1720**, 28–34.
82. Haraguchi, K. (2007) Nanocomposite hydrogels. *Curr. Opin. Solid St. M.* **11**, 47–54.
83. Sortino, S. (2008) Nanostructured molecular films and nanoparticles with photoactivable functionalities. *Photochem. Photobiol. Sci.* **7**, 911–924.
84. Johansson, E., E. Choi, S. Angelos, M. Liong and J. I. Zink (2008) Light-activated functional mesostructured silica. *J. Sol-Gel. Sci. Technol.* **46**, 313–322.
85. Slowing, I. I., B. G. Trewyn, S. Giri and V. S. Y. Lin (2007) Mesoporous silica nanoparticles for drug delivery and biosensing applications. *Adv. Funct. Mater.* **17**, 1225–1236.
86. Wu, C., C. Chen, J. Lai, J. Chen, X. Mu, J. Zheng and Y. Zhao (2008) Molecule-scale controlled-release system based on light-responsive silica nanoparticles. *Chem. Commun.* **23**, 2662–2664.
87. Weh, K., M. Noack, K. Hoffmann, K. P. Schroder and J. Caro (2002) Change of gas permeation by photoinduced switching of zeolite-azobenzene membranes of type MFI and FAU. *Microporous Mesoporous Mater.* **54**, 15–26.
88. Liu, N. G., D. R. Dunphy, P. Atanassov, S. D. Bunge, Z. Chen, G. P. Lopez, T. J. Boyle and C. J. Brinker (2004) Photoregulation of mass transport through a photoresponsive azobenzene-modified nanoporous membrane. *Nano Lett.* **4**, 551–554.
89. Angelos, S., E. Choi, F. Volgtle, L. De Cola and J. I. Zink (2007) Photo-driven expulsion of molecules from mesostructured silica nanoparticles. *J. Phys. Chem. C* **111**, 6589–6592.
90. Lu, J., E. Choi, F. Tamanoi and J. L. Zink (2008) Light-activated nanoimpeller-controlled drug release in cancer cells. *Small* **4**, 421–426.