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Photo-triggered molecular release based on auto-degradable polymer-containing organic–inorganic hybrids

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ABSTRACT

The photo-triggered molecular release from the organic–inorganic polymer hybrids is presented in this manuscript. Initially, the preparation of the auto-degradable polymer is explained with the photo-cleavable group at the end of the polymer main-chain. The silica-based dye-loaded hybrids containing these polymers were fabricated. It was found that by UV irradiation, the end capping was removed, and then the auto-degradation occurs through the polymer main-chain. Finally, the molecular release of the loaded dyes was accomplished in various media by the UV irradiation. In particular, it was shown that both of hydrophobic and hydrophilic dyes can be applied in this system.

1. Introduction

Photo-triggered controlled release is promising technology for developing a low-invasive therapy with fewer side effects.[1–6] Based on the well-designed inorganic scaffolds, the precise control of the molecular release has been also accomplished.[7,8] By regulating the timing of the light irradiation, the drug concentration at the local spot can be readily controlled with site- and time-specificities. For realizing practical system, a polymer-based scaffold which can capture the bio-active guest molecules without covalent-bond linking is a facile candidate as a platform for constructing a drug carrier.[9,8,10–15] In water phase, the hydrophobic moiety in the polymer scaffold can absorb the guests such as drugs or dyes, resulting in the encapsulation of the guests.[16–20] The water-solubility and stability against the undesired metabolism can be avoided. By preprogramming the photo-responsive system into the polymer matrix, the loaded molecules can be released by the trigger through light irradiation. Furthermore, we can receive the benefits from the nanomaterials. The site-specific delivery is possible by modulating the size of the polymer matrices.[21,22] Thus, it can be said that the polymer-based drug carriers are valid under diverse biological conditions. On the other hand, general polymers have relatively-low stability under biological conditions comparing to the inorganic materials. To improve the retention ability and to realize controlled release in long term, the development of robust scaffolds is desired.

Organic–inorganic polymer hybrids are classified as a mixture with a polymer and an inorganic material with the domain size at nano or molecular scale.[23] In general, the hybrid materials can show advant originated from both organic and inorganic elements. As a typical instance, by well-mixing with silicate, the robustness of the materials can be drastically and readily improved.[24–30] As a result, highly-emissive materials with high stability were obtained.[31,32] However, since the general hybrid materials have high environmental resistance, very few examples have been accomplished to offer the molecular release from the hybrids. Next challenge is to establish the stimuli-responsive release system using the hybrid materials with a wide variety of the guest molecules. In particular, we aim to receive the function such as wide encapsulation acceptability originated from organic polymers and high stability derived from the inorganic element.

Herein, we present the photo-triggered molecular release from the organic–inorganic polymer hybrids. Initially, we prepared the auto-degradable polymer with the photo-cleavable group at the end of the polymer main-chain and the silica-based dye-loaded hybrids containing these polymers. By UV irradiation, the end capping is removed, and then the auto-degradation occurs through the polymer main-chain. Finally, the molecular release of the loaded dyes was observed in the buffer by the UV irradiation. In particular, it was shown that both of hydrophobic and hydrophilic dyes can be applied in this system. This is the first example, to the best of our

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knowledge, to offer the photo-triggered molecular release from the organic–inorganic polymer hybrids.

2. Experimental section

2.1. General

^{1}H NMR and ^{13}C NMR spectra were measured with a JEOL EX-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer. Coupling constants (J value) are reported in hertz. The chemical shifts are expressed in ppm downfield from tetramethylsilane, using residual chloroform (δ = 7.24 in ^{1}H NMR, δ = 77.0 in ^{13}C NMR) as an internal standard. MASS spectra were obtained on a JEOL JMS–SX102A. UV–vis absorption spectra were obtained on a SHIMADZU UV3600 spectrophotometer using 1 cm path length cell. Luminescent spectra of the obtained hybrids were measured by a HORIBA JOBIN YVON FluoroMax-4 fluorescence spectrometer. All reagents were obtained from commercial sources and used as received without further purification.

2.2. Compound 2

Compound **1**[33] (2.5 g, 5.39 mmol) was suspended in a 31 mL of the mixture of THF/satd $NaHCO_3$aq/water (ratio 2:2:1). Phenyl chlorocarbonate (685 μL, 852 mg, 5.44 mmol) was added dropwise over 5 min. After stirring for 1 h, the reaction was monitored by TLC (EtOAc/hexane = 1:4). Methoxycyclopentane was added, and the organic phase was washed with satd $NaHCO_3$aq and brine. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:4). The crude product was recrystallized with toluene/heptane. Compound **2** was obtained as a white powder (2.33 g, 74%). ^{1}H NMR (DMSO-d_6): δ 9.40 (s, 0.3H), 9.30 (s, 0.7H), 7.47–7.7.38 (m, 3H), 7.17–7.12 (m, 2H), 6.86–6.73 (m, 4H), 6.42–6.36 (m, 2H), 5.23 (q, J = 6.0 Hz, 1H), 4.50 (s, 2H), 4.37 (s, 4H), 0.912 (s, 18H), 0.097 (s, 12H). HRMS (ESI): m/z calcd for $C_{32}H_{49}NO_5Si_2$+NH_4^+ (M+NH_4^+): 601.3488. Found: 601.3487.

2.3. P1

Compound **2** (1.0 g, 1.71 mmol), 4,5-dimethoxy-2-nitrobenzyl alcohol (73 mg, 0.34 mmol) and DBTL (5 mol %) were dissolved in dry DMSO (3.43 mL) and heated at 115 °C under argon atmosphere. The solution was stirred for 45 min. After cooling to room temperature, the polymer was precipitated from methanol, filtered and dried under reduced pressure for a few hours. The polymer **P1** was obtained as a white powder (868 mg, M_n = 16000, M_w = 20000, 95%). This polymer is soluble in THF. ^{1}H NMR (THF-d_8): δ 10.7 (s), 7.51 (br) 7.41 (s), 6.81 (br), 6.22 (br), 5.05 (br), 4.49 (d), 4.28 (br), 0.86 (s), 0.07 (s).

2.4. Preparation of hybrids films

Hybrid films were prepared by the acid-catalyzed sol–gel reaction of methyltetramethyl orthosilicate (MeTMOS) using 0.1 M HCl aqueous solution. Polymer **P1** was dissolved in DMF (200 mg/L), HCl, and MeTMOS was added. After stirring for 5 min, the reaction solution was poured into a polypropylene vessel, and then heated at 60 °C for 2 days. The transparent hybrid films were obtained.

2.5. Preparation of hybrids containing dyes

Hybrids films containing boron dipyrromethene (BODIPY) and fluorescein dyes were prepared by the acid-catalyzed sol–gel reaction of tetramethyl orthosilicate (TMOS) using 0.1 M HCl aqueous solution. Polymer **P1** was dissolved in DMF (20 mL, 200 mg/L), HCl (0.3 mL) was added, followed by TMOS (3 mL). After stirring for 5 min, different amounts of a solution of BODIPY (0.21 mM) in THF (1 mL) or fluorescein (1 mM) in DMF were added to the reaction solution. The reaction solution was poured into a polypropylene vessel and then heated at 60 °C for 5 days. The glassy green colored hybrid blocks were obtained. The total amount of the dyes is corresponded to the dye concentration in the solution in the sol–gel reaction.

2.6. UV irradiation

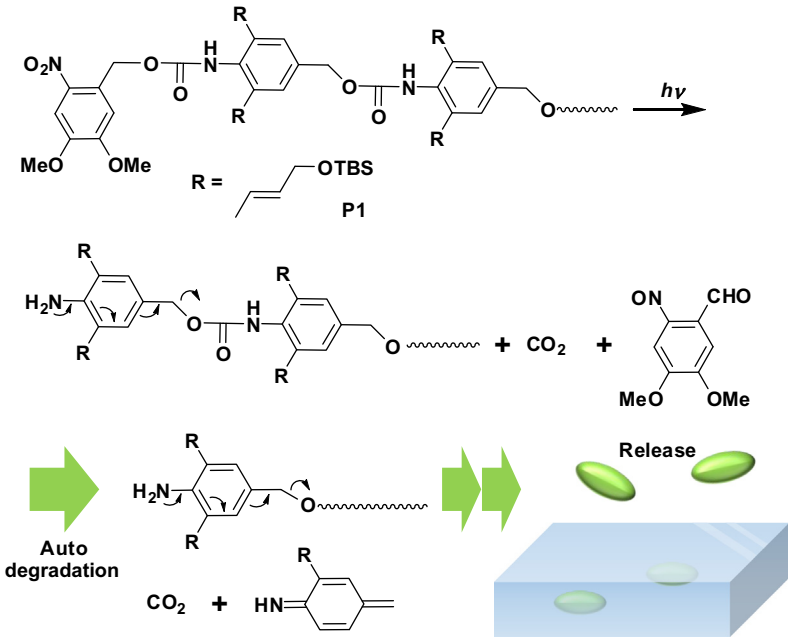
The reaction mixture and hybrids were irradiated with a trans-illuminator, LMS-20E (365 nm ± 20 nm, 6.5 mW/cm^2), at 25 °C in open air for each time above 10 cm on the stage.

3. Results and discussion

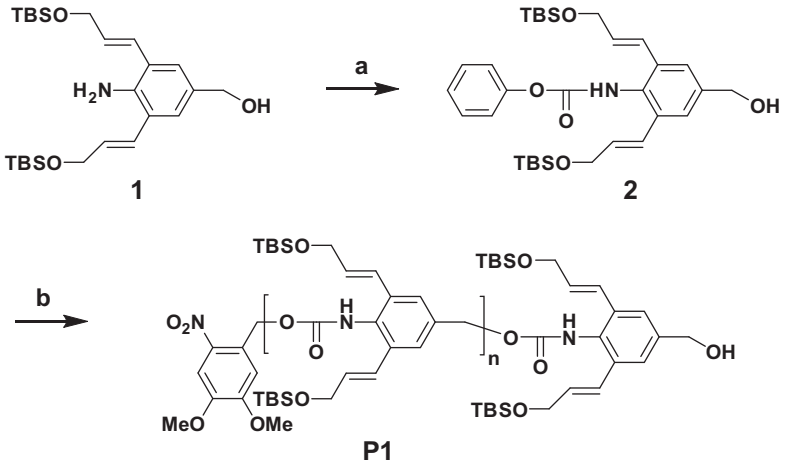
The chemical structure and molecular release based on the hybrid material containing the photo-induced auto-degradable polymer are shown in Scheme 1.[33–39] By UV irradiation, the *o*-nitrobenzyl ether moiety is released, followed by the generation of the amino group. Electron donation of the amino group induces the release of the monomer unit at the end of the main-chain, resulting in the generation of the new amino group. The detachment can proceed at the end of the polymer chains, and finally all of the polymer main-chains are fragmented. The auto-degradation systems were used in biotechnology such for labelling of the proteins.[33] Therefore, the toxicity of our polymers could be the similar level to the previous materials. Moreover, by employing the auto-degradable polymer, the quantum yield of photo-reaction can be amplified, leading to the suppression of the amount of the harmful byproducts such as nitroso species. It is proposed that the polymer element forms the domain structures in the nanoscale in the hybrids.[40] The loaded hydrophobic molecules tend to be distributed in the polymer-rich domains.[40] Therefore, after the fragmentation of the polymer main-chains, it is assumed that the encapsulated ability of the hybrid materials should drastically decreased. As a result, the hydrophobic encapsulated molecules can be released. In this study, the two kinds of fluorescent dyes are loaded into the hybrids to quantitatively analyze the amount of the released molecules after the photo irradiation.

The synthesis of the monomer and polymer **P1** was performed by employing our previous report as outlined in Scheme 2.[33] To improve the solubility, the TBS groups were introduced into **P1** at the side chains. In the presence of dibutyltin dilaurate (DTDL) as a catalyst and 4,5-dimethoxy-2-nitrobenzyl alcohol as an end cap, the polymerization was carried out. Although we also tried polymerization reaction in the absence of the end-capping, the products with smaller molecular weights were obtained. It is presumed that the polymer without the end capping could be instable due to the auto-degradable process. The number-average molecular weight (M_n) of the product was estimated as 16,000 by gel permeation chromatography (GPC, polystyrene standards, DMF eluent). The synthesized polymer **P1** showed good solubility in organic solvents such as DMF and DMSO. After reprecipitation in methanol, **P1** was collected. From ^{1}H NMR analysis, it was confirmed that **P1** had the desired chemical structure as we designed.

To evaluate the photo-cleavable reactivity of the end caps in the polymer, the time-course of the spectrum change in UV–vis absorption was examined with variable time of UV irradiation (Fig. 1). By increasing UV irradiation time, the absorption band around 350 nm assigned as the nitro group decreased.[33] In addition, the absorption band around 400 nm increased. According to the previous reports, these data mean the generation of the



Scheme 1. Chemical structure of materials and proposed mechanism for molecular release triggered by light-driven auto-degradation of polymers in hybrid materials.



Scheme 2. Synthesis of **P1**. Reagents and conditions: (a) Phenyl chloroformate, THF/satd·$NaHCO_3$aq/water, rt 1 h, 74%; (b) dibutyltin dilaurate, 4,5-dimethoxy-2-nitrobenzyl alcohol, DMSO, 115 °C, 40 min. $M_w = 2.0 \times 10^4$, $M_n = 1.6 \times 10^4$. TBS = *tert*-butyldimethylsilyl.

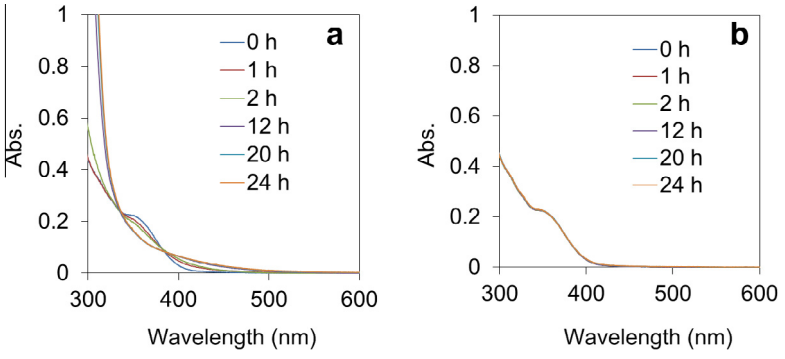


Figure 1. Time-courses of the changes in UV–vis spectra of **P1** solution (0.2 g/L) in DMF (a) with and (b) without UV irradiation.

nitroso compound which is the degradation product from *o*-nitrobenzyl ether in the photoreaction.[33] Within 20 h, the starting material was completely consumed. Without UV irradiation, the spectrum changes were hardly observed. From these results, it is indicated that the synthesized can be activated by UV irradiation.

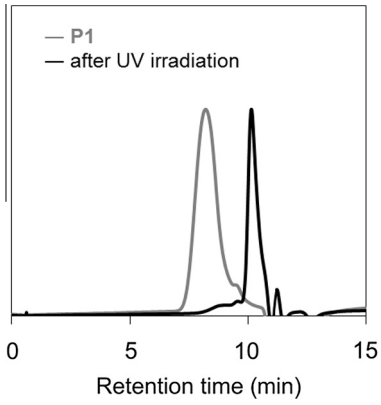


Figure 2. GPC profiles of **P1** before (gray line) and after (black line) the UV irradiation.

The photo-degradation was monitored by GPC (polystyrene standards, DMF eluent). After UV irradiation for 24 h, the M_n of the polymer was significantly reduced from 16,000 to 2000 (Fig. 2). The M_n of the monomer was determined as 2500 under the same solvent condition. This result directly indicates that degradation of the polymer should occur after UV irradiation. In our previous report, it was observed that the molecular release at the *para* position toward the amino group can occur immediately just after removing the end-cap group. The degradation rate of the main-chain was much faster than that of the photo-cleavage of the end cap. Thereby, the reaction rate was not determined.

The hybrid materials were prepared via the acid-catalyzed sol–gel method.[41] The reaction mixture containing 0.1 M HCl aq, TMOS, and the synthesized polymer in DMF was heated with an oven at 60 °C for 5 days. The transparent hybrids were obtained without aggregation of the dyes (Fig. 3). In previous reports, it is known that BODIPY can readily form the aggregation, resulting in the color changes to orange, while such unfavorable changes were less observed.[41] From the microscopic observation, the phase separation or cracks were hardly detected. These data indicate that the homogeneous hybrids can be prepared. In the presence of the dyes, transparent hybrids can be also obtained. Although we also applied other alkoxysilanes such as phenyl-, methyl-, and octyltrimethoxysilanes, in the sol–gel reaction, the fragile fragments were obtained. Consequently, it was found that the transparent colored materials can be obtained only with TMOS. By using ammonium hydroxide as a catalyst, the homogeneous hybrid was not obtained. It is assumed that **P1** could be decomposed under the basic condition.

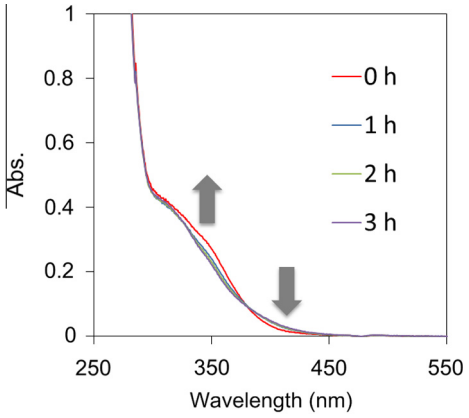


Figure 4. UV–vis spectra of hybrid film with UV irradiation.

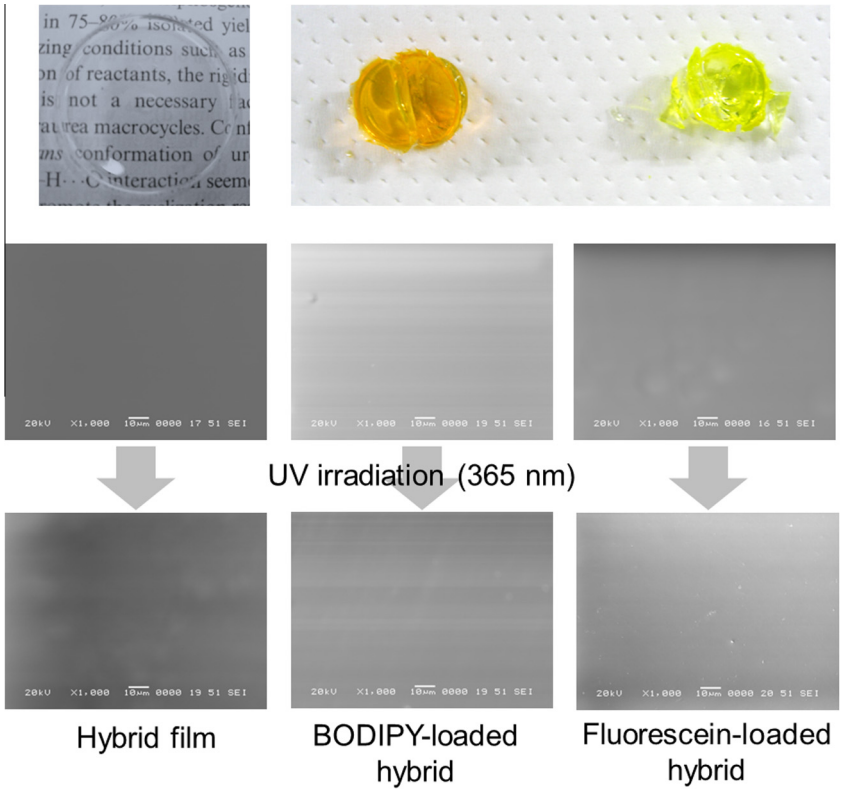


Figure 3. Appearances (top) and SEM observations before (middle) and after (bottom) the UV irradiation at 365 nm. The scale bars represent 10 μm.

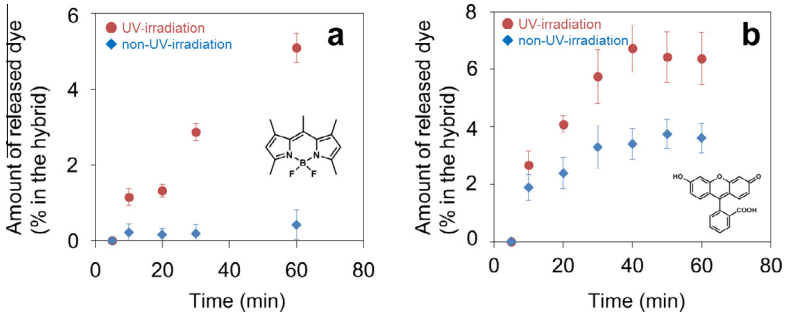


Figure 5. Amount of released (a) BODIPY in THF and (b) fluorescein in water. The plots were obtained from the averages of three data sets. The error bars mean standard deviation.

To evaluate the photo reactivity of the polymer in the hybrid film, the time-course of the spectrum change in UV–vis absorption of the hybrid film was monitored with variable time of UV irradiation (Fig. 4). Initially, it was observed that the absorption spectra of the hybrids showed good agreement with that of **P1** in the solution. These data mean that **P1** can be incorporated into the hybrid without degradation. Corresponded to the results in the solution, the absorption band around 350 nm and 400 nm attributed to the generation of the nitroso compounds increased by increasing UV irradiation time.[31] These data mean the end capping of the polymer main-chain was cleaved by the light irradiation. Considering the result from the degradation behavior of the polymer in the solution, the subsequent main-chain degradation could occur in the hybrids. Without the UV irradiation, the significant changes were hardly detected at least after the storage for one week in the air. It is suggested that only the UV irradiation could induce the auto-degradation of the polymer main-chains.

Finally, the photo-triggered release of the guest molecules from the hybrids was performed (Fig. 5a). We prepared the two kinds of the dye-loaded hybrids containing the auto-degradable polymers. The changes in the amount of the released dyes in the media were plotted. Initially, boron-dipyrromethene (BODIPY) was introduced into the hybrid, and the releasing behavior was evaluated. BODIPY derivatives are well known as a fluorophore with suitable optical properties as a bioprobe such as high emission quantum yield, large absorption, and high stability under biological conditions. However, because of extremely poor solubility, the aggregation of BODIPY molecules readily proceeds in the polar solvents, resulting in the spoil of optical properties. With the sol–gel reaction as shown above in the presence of a BODIPY dye, the homogeneous material can be obtained. The UV light (254 nm) was irradiated for 2 days in open air. The sample was levigated, and 10 mg of the powder was immersed into THF. The amount of dyes released into the solution was estimated from the emission intensity of the dye from the filtrate. From the sample without UV irradiation, the released BODIPY was hardly detected. On the other hand, the BODIPY dye was observed from the sample with UV irradiation. These data clearly indicate that BODIPY can be released from the hybrids triggered by the light irradiation. In water phase, the molecular release slightly occurred. It is likely that BODIPY should be adsorbed at the surface of the hybrid because of the strong hydrophobicity.[42]

By using fluorescein as a fluorophore, the similar experiment was performed (Fig. 5b). The UV light was irradiated to the fluorescein-loaded hybrid for 2 days at room temperature, and the levigated sample was soaked into water. The emission intensity in the filtrate was evaluated with a fluorescence spectroscopy. By UV irradiation, the molecular release from the hybrids was obviously induced. Fluorescein is more water-soluble than BODIPY. Therefore, the slight release was observed from the sample without UV irradiation. These data including the results with BODIPY indicate that the synthesized hybrids containing the auto-degradable polymer can release the loaded guest molecules triggered by the light irradiation. As shown in Figure S1, the emission intensities from both samples with or without UV irradiation were compared. If the photodegradation occurs, the amount of the released dyes should be apparently reduced in the UV-irradiated samples, whereas we obtained the similar intensities from the samples with or without UV irradiation. These data represent that the loaded dyes were protected from the photodegradation in the hybrids. The encapsulation by the hybrid can enhance the stability to the encapsulated guest molecules as often observed in the hybrids or the silica-based materials.[42] The powder samples were prepared with mechanical levigation. By using the nanoparticles, the amount of the released dyes could be improved.

4. Conclusion

The photo-triggered molecular release from the organic–inorganic polymer hybrids is demonstrated in this manuscript. The silica-based dye-loaded hybrids containing these polymers were prepared. It was shown that the molecular release of the loaded dyes occurred in various media triggered by the UV irradiation. Moreover, both of hydrophobic and hydrophilic dyes can be used in this system. It is proposed that hybrid-based molecular release possesses the advantages derived from both organic and inorganic elements: By altering the type of polymers, the release rate and the amount of the loaded dye molecules could be controlled. As shown in this study, the stability of the loaded dyes can be enhanced owing to the inorganic element. Thus, the hybrid-based molecular carrier for drug release is promised to be versatile for various biological events and conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2014.04.034.

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