Hindawi Publishing Corporation
Journal of Nanomaterials
Volume 2016, Article ID 4964693, 7 pages
http://dx.doi.org/10.1155/2016/4964693

Research Article

Light-Regulated Release of Entrapped Drugs from Photoresponsive Gold Nanoparticles

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Received 15 September 2015; Accepted 30 December 2015

Academic Editor: Rajesh R. Naik

Release of a payload in a spatiotemporal fashion has a substantial impact on increasing therapeutic efficacy. In this work, a novel monolayer of gold nanoparticles (AuNPs) featuring light-responsive ligands was investigated as a potential drug carrier whose drug release can be triggered by UV light. Hydrophobic molecules were noncovalently entrapped in the compartments of its monolayers. Once irradiated with UV light, the dinitrobenzyl linker was cleaved, leading to release of the entrapped agent. AuNPs were characterized using UV spectrophotometry, TEM, and a zetasizer. A naturally occurring compound extracted from *Goniothalamus elegans* Ast was chosen as a hydrophobic model drug. Entrapment and release of dye were monitored using fluorimetry. The percent encapsulation of dye was of 13.53%. Entrapped dye can be released upon UV irradiation and can be regulated by changing irradiation time. Up to 83.95 ± 2.2% entrapped dye can be released after irradiation for 20 minutes. In the absence of UV light, dye release was only 19.75%. For comparison purposes, AuNPs having no dinitrobenzyl groups showed a minimal release of 12.23% and 11.69% with and without UV light, respectively. This demonstrated an alternative strategy to encapsulate drugs using a noncovalent approach followed by their controlled release upon UV irradiation.

1. Introduction

The use of nanomaterials as drug carriers has a profound impact on nanomedicine [1]. Nanocarriers such as liposomes [2], dendrimers [3], micelles [4], polymeric nanoparticles [5], and gold nanoparticles [6] show very good promise in drug delivery applications due to their capabilities in enhancing therapeutic efficacy. However, release of drugs from carriers remains a key challenge for clinical applications. To solve drug release problems, responsive materials have been widely investigated [7]. Several triggers for drug release have been proposed including temperature [8], pH [9], redox enzymes [10], ultrasound [11], and light [12]. Among a variety of stimuli, UV light has been considered highly attractive in the controlled release of drugs [13], DNA, protein [14], and signaling agent applications [15]. Light-regulated gold nanoparticles have demonstrated potential as agents for use in regulation of biological-macromolecules and drug delivery systems. Han et al. demonstrated the use of UV light to regulate DNA/gold nanoparticles [16]. Agasti et al. utilized light to

cleave dinitro benzyl linkages, releasing 5-fluorouracil from a monolayer in MCF-7 cells [17]. Drugs and/or cellular signal molecules can be tagged with photo sensitive groups, creating a caged compound which is essentially biologically inert. Upon irradiated, the caged compound can be reactivated and transform to an active biologically compound.

AuNPs have shown great potential for use as drug delivery platforms [18]. AuNPs have a number of advantages including their ease of surface modification, biocompatibility, chemically inert nature and minimal toxicity [19]. Additionally, a wide range of core sizes can easily be fabricated. The monolayers of AuNPs are composed of interior hydrophobic pockets and an exterior hydrophilic shell. The chemical composition of their monolayers of AuNPs are of a similar structure to those of micelles [20]. Kim et al. reported the incorporation of hydrophobic drugs such as lapachone and tamoxifen into the zwitterionic monolayers of AuNPs, providing an alternative delivery strategy with the potential for avoiding premature drug release and prodrug processing issues [21]. Lucarini et al. reported that para-substituted benzyl hydroxyalkyl nitroxides can be entrapped in the hydrophobic portion of a monolayer [22]. The packing of the monolayer onto the surface of gold nanoparticles decreased with decreasing in size of nanoparticles size due to increasing the curvature of their gold cores. As a result, monolayers were bound to small nanoparticles by an alkyl chain, thereby creating a hydrophobic pocket to host a hydrophobic guest molecule. Due to their nanosized characteristics, AuNPs can preferentially accumulate at tumor sites through the leaky tumor neovasculature known as "enhanced permeability and retention" (EPR) effect [23]. Noncovalent approaches can serve drugs in an active form which could be readily released at the site of action. The release of a drug from a noncovalent bond still lacks control and remains a challenge. Therefore, designing AuNPs with dinitrobenzyl group that can be used to host drugs and release of drug is of great interest.

In this work, we aim to investigate the controlled release by UV light of a model of drug which was noncovalently entrapped inside the monolayers of AuNPs. The design of an alkanethiol monolayer composed of hydrophobic pockets coupled with the aromatic character of dinitrobenzyl groups could provide more space to host a hydrophobic drug, referred to Au-PC-COOH (Figure 1). The exterior of the monolayer was the anionic carboxylate group, which can minimize nonspecific binding to biomacromolecules and promote an EPR effect [24]. As a control experiment, the gold nanoparticles with a similar ligand to PC-COOH, but with no dinitro benzyl units was fabricated, referred to Au-COOH. AuNPs were characterized using transmission electron microscopy (TEM), UV-vis spectrophotometry, and zeta potential analysis. The release of a model drug *in vitro* was done using a system with a two-phase solution.

2. Experimental

2.1. Fabrication of Au-PC-COOH Nanoparticles. Gold nanoparticles were synthesized and subjected to ligand displacement via a procedure employing the Brust-Schiffrin method [25] and the Murray place exchange [26], respectively. $HAuCl_4$ (30 mM) was suspended in DI water (30 mL) and placed in a 250 mL round bottom flask in which a clear solution was produced after 10 min of stirring. Tetraoctylammonium bromide (50 mM) in 80 mL of toluene was added to the solution. 170 mg of 1-dodecanethiol and 25 mL of 0.4 mM of sodium borohydride in 25 mL of DI water were added to the reaction, respectively. The reaction was allowed to continue for 3 h at room temperature under constant stirring. The organic layer was collected and subjected to rotary evaporator. Washing with ethanol (400 mL × 3) was done to remove the excess free ligand and precipitate in cold ethanol. Gold nanoparticles were characterized using TEM (FEI Tecnai G2 20). These particles were called Au-C_{12}.

Au-PC-COOH was prepared using a place-exchanged reaction of Au-C_{12}. Au-C_{12} (0.0307 g, 0.104 mmol) was suspended in dichloromethane (5 mL) and placed in a 25 mL round bottom flask. A solution of thiolated PC-COOH ligands (0.3351 g, 1.04 mmol) was suspended in methanol (1 mL) and added to the Au-C_{12} solution. The solution was flushed with nitrogen throughout reaction. The reaction was allowed to continue for 48 h at room temperature under constant stirring. The volatile solvent was distilled under reduced pressure and washed with hexane (3 × 15 mL) to remove the excess free ligand and then was evaporated under reduced pressure yielding a dark residue. DI water was added to this residue. NaOH (1 M) was gently added to suspend the Au-PC-COOH. Gold nanoparticles were characterized using transmission electron microscopy and UV-vis spectrophotometry (Shimadzu, UV-1800). These particles were referred to as Au-PC-COOH.

2.2. Photoresponsive Property of Au-PC-COOH. A solution of Au-PC-COOH (0.23 μM, 3010 μL) in PBS buffer was irradiated using a hand-held UV light source (~365 nm) for one of several predetermined times (5, 10, 20, 30, 40, 50, and 60 min). After irradiation, the absorbance behavior of the solution between 300 and 600 nm was recorded.

2.3. Entrapment of Dye into Hydrophobic Pockets of Au-PC-COOH. Entrapment of hydrophobic dye into the hydrophobic pockets of Au-PC-COOH was done using a solvent evaporation method. A naturally occurring compound was chosen (see Figure 1) as a hydrophobic model drug. It was a dye extracted from the bark of *Goniothalamus elegans* Ast. This substance had a promising cytotoxicity against the KB, MCF7, and NCI-H187 cell lines [27]. Dye (0.5 mg) was dissolved in 1 mL of acetone. Au-PC-COOH (20 μM, 500 μL) in PBS buffer and dye (0.1 mg, 200 μL) were thoroughly mixed and stirred for 24 h. The mixture was then subjected to evaporation using a rotary evaporator to remove acetone. After evaporation, the excess of hydrophobic dye was precipitated. The mixture was filtered several times using a membrane (0.45 μm) and subjected to dialysis for 24 hours until no free dye was observed.

Encapsulation of dye was quantified using DL-dithiothreitol (DTT) to drive disulfide ligand exchange. A solution of Au-PC-COOH (2 μM, 400 μL) was treated

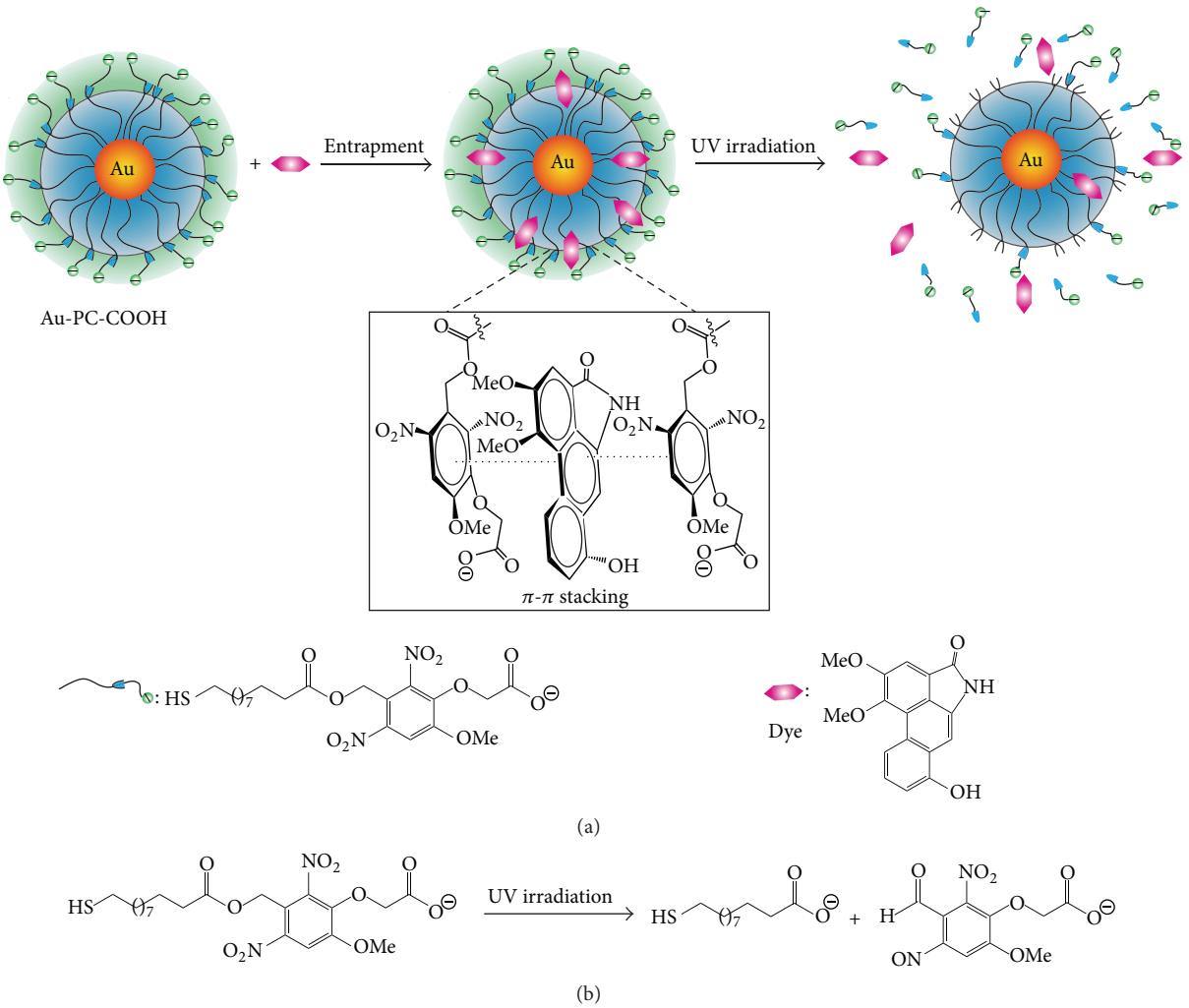

FIGURE 1: (a) Structure of Au-PC-COOH loaded with dye, structure of dye, and release of payload using UV light, (b) photocleavage reaction of a PC ligand.

with DTT (100 μM, 400 μL) and stirred for 360 min. After a predetermined time, toluene (1200 μL) was added to the solution to yield a two-phase solution. The toluene phase (1000 μL) was pipetted out and its fluorescent intensity measured. The amount of dye remaining was determined using fluorescent spectrophotometry (JASCO, FP-8200, excitation = 341 nm, and emission = 484 nm). Release studies were done in triplicate. The amount of released dye was determined according to a standard curve constructed using different concentrations of dye.

2.4. Phototriggered Release of Entrapment Dye in PBS Solution. Au-PC-COOH solution (1 μM, 2 mL) was irradiated using a hand-held UV lamp emitting at a wavelength 365 nm for 0, 5, 10, 15, and 20 min. After the predetermined time (5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 min), 1200 μL of toluene was added to form a two-phase toluene-aqueous system. The toluene portion was separated and its fluorescence intensity determined.

Au-COOH was fabricated and used as a control experiment. Dye encapsulation and release were done according the same protocols described for Au-PC-COOH.

3. Results and Discussion

3.1. Morphology of Au-PC-COOH. Au-PC-COOH was characterized through transmission electron microscopy (TEM) as shown in Figure S1(a) (see Figure S1(a) in Supplementary Material available online at http://dx.doi.org/10.1155/2016/4964693). The size of Au-PC-COOH was determined from randomly selected images using the Image J program. The size of Au-PC-COOH particles was found to be 2 ± 0.2 nm (Figure S1(b)).

3.2. Photoresponsive Property of Au-PC-COOH. The dinitrobenzyl groups are stable under ambient light conditions. Upon exposure to UV light (365 nm), photolytic cleavage

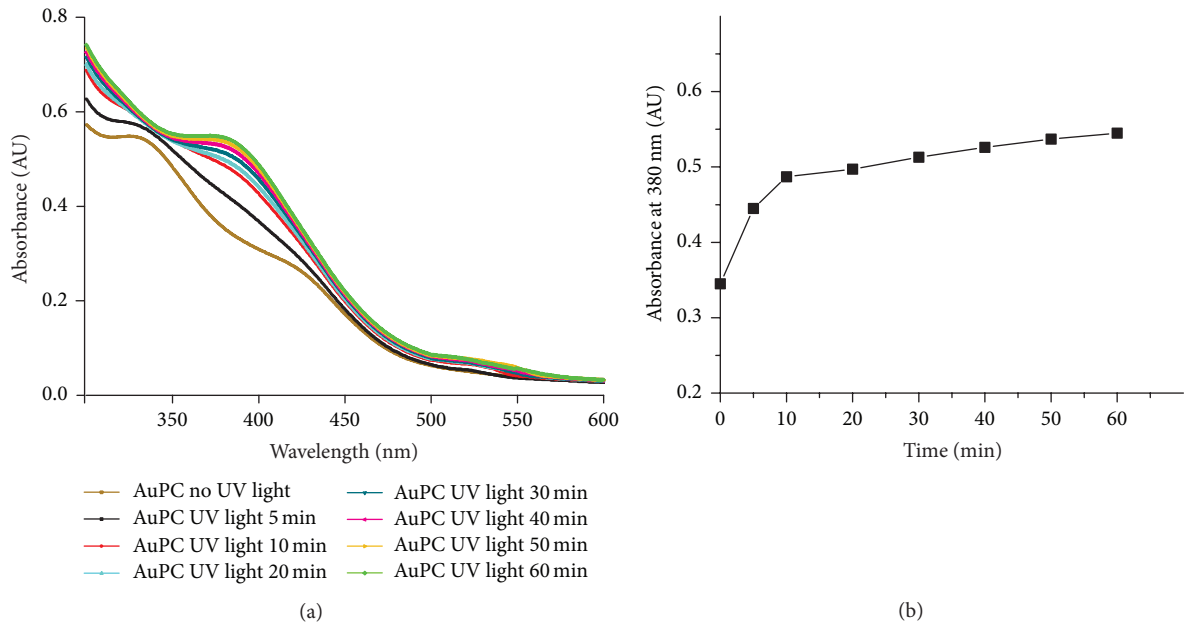

Figure 2: (a) UV-vis spectra of Au-PC-COOH (1 μM) in PBS solution under UV irradiation at 365 nm for different times, (b) plot of absorbance at 380 nm against UV irradiation time.

occurs. The photoresponsive property of Au-PC-COOH in PBS (pH ~ 7.4) was tested and monitored using a UV spectrophotometer. Figure 2(a) shows absorbance of Au-PC-COOH under irradiation for various periods of time (0–60 minutes). UV absorbance was observed at 380 nm, which corresponds to *o*-nitro-benzaldehyde compounds that occurred in the photochemical reaction. The main peak at 380 nm increased with increasing irradiation time, indicating that the *o*-nitro-benzaldehyde compounds were released from the monolayer. As a result, the remaining monolayer was diminished (Figure 1(b)). Figure 2(b) shows absorbance versus irradiation time. It is notable that dinitro benzyl linkers were cleaved very fast, requiring 5 to 10 minutes of irradiation time. After that, the photochemical reaction slowed and leveled off after 10 minutes. This indicated that dinitrobenzyl groups were gradually breaking their photolabile ester bonds with Au-PC-COOH. Likewise, the UV-vis spectra of the dinitro benzyl ligand in PBS buffer (1 mg/mL) showed a similar characteristic with UV irradiation time (Figure S2). UV-vis spectrum of a ligand solution changes was also observed at a wavelength of 380 nm, indicating a photoreaction and release of nitroso benzaldehyde compounds.

The mean particle sizes of Au-PC-COOH pre- and postentrapment were 6.38 ± 1.11 nm and 6.67 ± 1.74 nm, respectively. To test a stability of colloidal Au-PC-COOH, a zeta potential measurement was done using a Malvern nano ZS. The zeta potentials were measured in triplicate and an average zeta potential value of Au-PC-COOH was found to be −43.1 ± 1.64 mV. In general, stability of colloidal nanoparticles is dependent on the charge of the nanoparticles. The zeta potential is an indicative of the stability of colloidal gold in solution through an electrostatic repulsion of nanoparticles with the same charge. Nanoparticles with zeta potential values of more than ±30 mV are normally considered stable and well-dispersed in solution without aggregation and precipitation [28]. The Au-PC-COOH particles were stable for more than a month.

3.3. Entrapment of Dye in Hydrophobic Pockets. Next, entrapment of the dye was studied. The dyes were entrapped using a solvent displacement method as described above. The amount of loaded dye was quantified using DL-dithiothreitol (DTT) as a triggering agent. DTT is widely known to be capable of highly efficient exchange of ligands from gold nanoparticles [29]. The encapsulation efficiency (EE%) of dye in the monolayer of Au-PC-COOH was calculated as follows:

$$\text{Encapsulation efficiency (EE\%)} = \left(\frac{W_t}{W_i}\right) \times 100\%, \quad (1)$$

where W_t is the total amount of dye entrapped in the monolayers and W_i is the total quantity of dye initially added. The entrapped dye was found to be 13.53%. This result is comparable to that of a drug in polymeric micelles [13]. The Au-PC-COOH loaded with the dye was also stable for more than a month.

3.4. Phototriggered Release of Entrapment Dye in PBS. To explore the release of the model drug payload *in vitro*, release of entrapped dye was determined as a function of UV exposure time and monitored through fluorescent spectrophotometry. We hypothesized that this novel photocleavable ligand could effectively bind with the payload, avoiding premature drug release due to π-π stacking [30] and hydrophobic-hydrophobic interaction [22]. Au-PC-COOH solution (1 μM, 2 mL) was irradiated using a hand-held UV

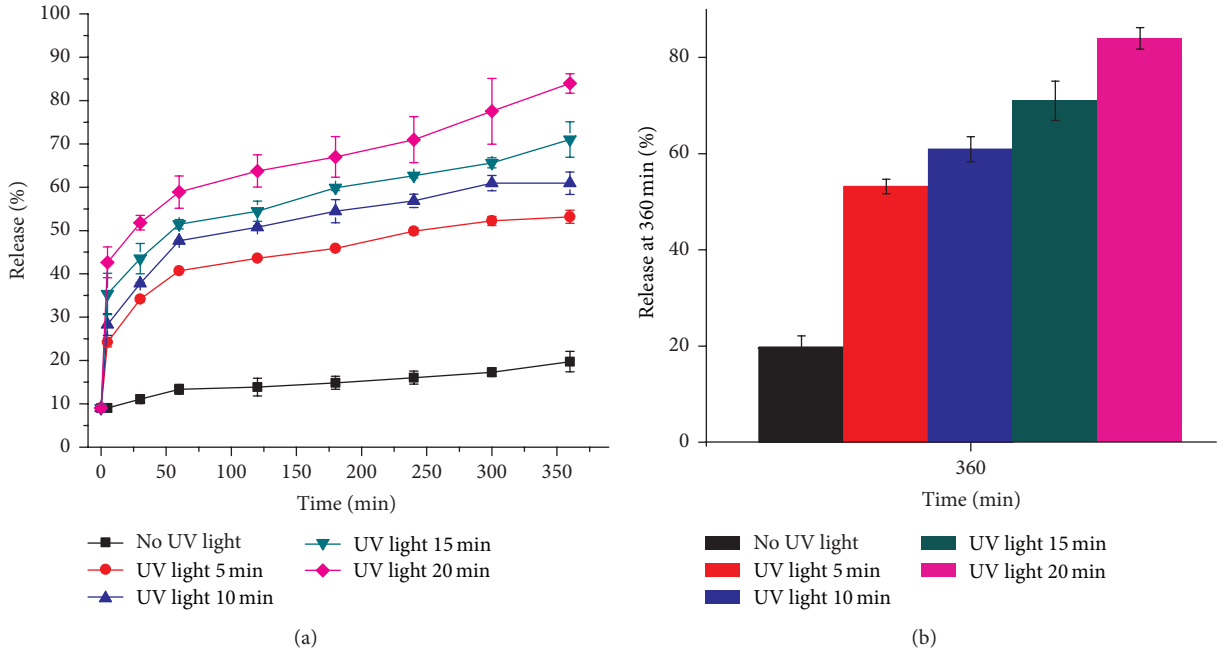

Figure 3: (a) Cumulative release profiles of dye from Au-PC-COOH in PBS solution (1 μM, pH ~ 7.4) after UV irradiation for 5, 10, 15, and 20 minutes, (b) % release of dye recorded after 360 minutes after UV irradiation for 5, 10, 15, and 20 minutes.

lamp emitting at a wavelength 365 nm for 0, 5, 10, 15, and 20 min. Figure 3(a) shows percent release of dye versus time. A rapid release was observed upon UV irradiation. The dye was detected at levels of 24.22%, 28.31%, 35.35%, and 42.65% within 5 minutes after irradiation for 5, 10, 15, and 20 min, respectively. The release rates gradually increased with exposure time. Longer UV exposure times gave higher release of dye. The latter stage may proceed due to diffusion of the dye outward from the monolayer. When the nitrobenzaldehyde unit was cleaved, a lack of π-π interaction possibly occurred, resulting in no functional group holding the dye inside a monolayer. The cumulative drug release of neutral dye was up to 53%, 60%, 71%, and 83% within 360 min after irradiation of the nanoparticles for 5, 10, 15, and 20 min, respectively (Figure 3(b)).

Glutathione (GSH) causes ligand displacement from gold nanoparticle surfaces at both intracellular and extracellular levels [31]. Intracellular glutathione can cause the release of drugs from these particles through a versatile place-exchanged mechanism. We then used GSH as a cooperative drug triggering agent. The release of dye under cotriggered conditions was 68% in 5 minutes and increased to 90% in 360 minutes (Figure 4(a)). When compared with the use of either UV light or GSH alone, this cotriggered condition further facilitated the release of dye.

As a control experiment to validate the role of a dinitro benzyl unit, a monolayer of AuNPs with a similar chemical structure to that of Au-PC-COOH ligands but having no dinitro benzyl linkers was fabricated and referenced as Au-COOH. The dye was entrapped in the monolayer of Au-COOH using the protocol described above. The amount of loaded material was found to be 15.3%. The average particle sizes of Au-COOH pre- and postentrapment were 6.49 ± 1.42 nm and 6.71 ± 1.87 nm, respectively. Then, drug release from Au-COOH under UV irradiation was determined. Under UV irradiation for 5 min, it was observed that the dye released from the monolayer was negligible and found to be about 12.23% over the entire 360 minutes. In the case of no UV irradiation, the release of dye was of 11.69% (Figure 4(b)). This result shows that dinitro benzyl linkers have an important role in controlling the release of dye in the presence of UV light (Figure 4(c)).

4. Conclusions

We demonstrated a novel monolayer of gold nanoparticles that was used to study the controlled release of a model drug using UV light. The role of dinitrobenzyl units is substantial in the controlled release of an entrapped model drug. These anionic nanoparticles host a hydrophobic dye in a hydrophobic pocket. Upon irradiation, the monolayer of Au-PC-COOH was cleaved, thus resulting in dye release. UV light provides a higher release of drugs compared to a system exposed to no UV radiation. Upon UV irradiation, an encapsulated model drug was released over time. The release of dye can be controlled by controlling UV irradiation. Surface modification and the ease of model drug entrapment coupled with the controlled release of drug in a spatiotemporal manner is a promising strategy for delivering therapeutic materials to the site of diseased tissue.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

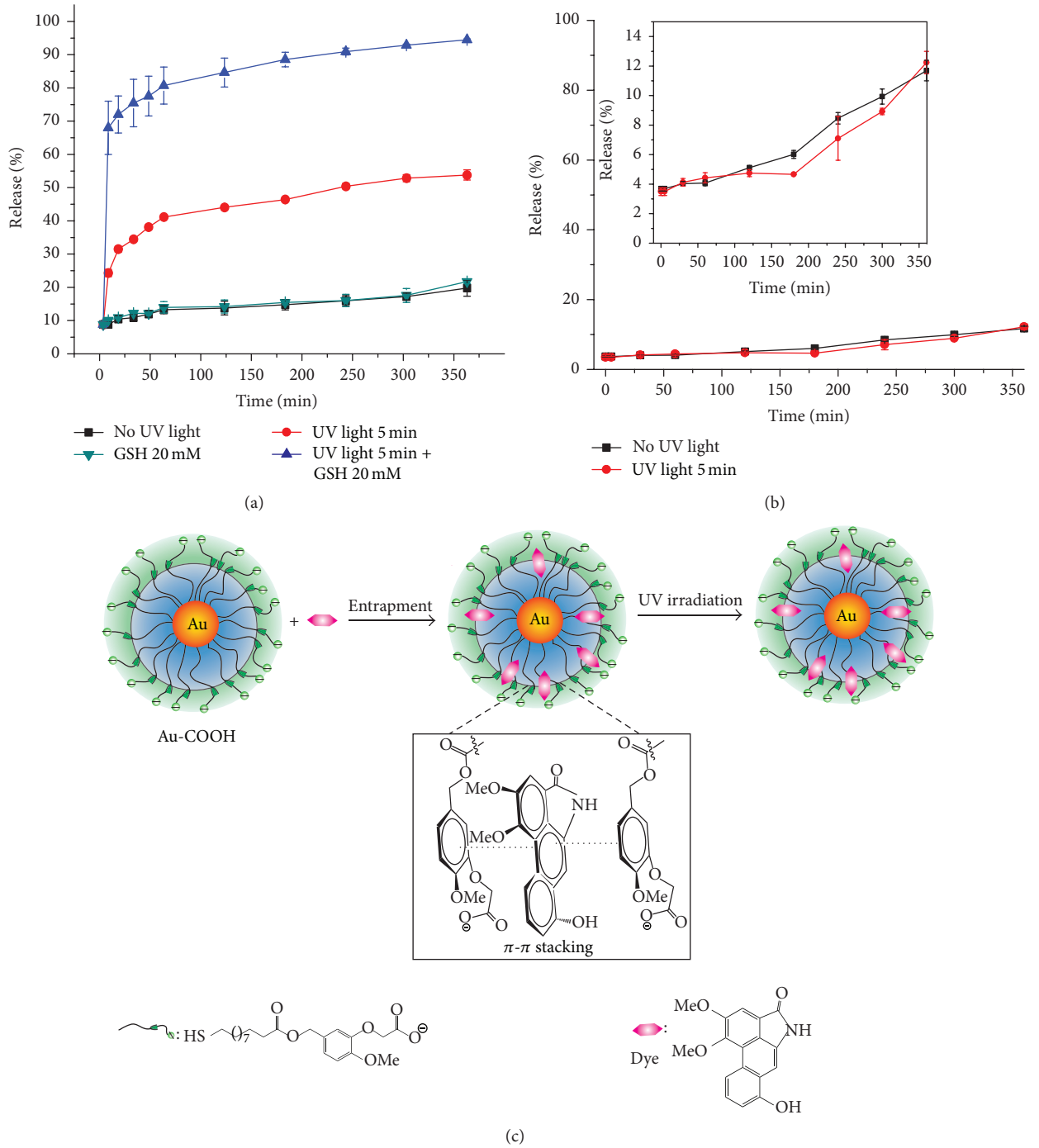

FIGURE 4: (a) Cumulative release profiles of dye from Au-PC-COOH in PBS solution (1 μM, pH ~ 7.4) without UV light, glutathiones (20 mM), UV irradiation for 5 minutes, and UV irradiation for 5 minutes + glutathiones (20 mM). (b) Cumulative release profiles of dye from Au-COOH in PBS solution (1 μM, pH ~ 7.4) without UV light, UV irradiation for 5 minutes (inset: high magnification of cumulative release profiles of dye). (c) Structure of Au-COOH loaded with dye, structure of dye, and release of payload using UV light.

Acknowledgments

Kaniknun Sreejivungsa would like to thank the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission for her M.S. scholarship. The authors would like to acknowledge the financial support by the Institute for the Promotion of Teaching Science and Technology (IPST), the Nanotechnology Center (NANOTEC), NSTDA, Ministry of Science and Technology, Thailand, through its program of Center of Excellence Network, and Khon Kaen University under Incubation Researcher Project.

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