# Switchable on/off drug release from gold nanoparticles-grafted dual light- and temperature-responsive hydrogel for controlled drug delivery

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**Abstract:**

A switchable dual light- and temperature-responsive drug carrier using gold nanoparticles (Au NPs)-grafted poly (dimethylacrylamide-co-acrylamide)/poly acrylic acid [(P(DMA-co-AAm)/PAAc] hydrogel was prepared by free radical polymerization procedure using N, N-methylenebisacrylamide as cross-linker and ammonium persulfate as initiator. Initial P(DMA-co-AAm) hydrogel and uniformly-distributed stable Au NPs, prepared by reduction of hydrogen tetrachloroaureate (III) hydrate in the presence of trisodium citrate, were synthesized separately. Then, the prepared P(DMA-co-AAm) and Au NPs were added to an acrylic acid solution along with the cross-linker and initiator to prepare PAAc hydrogel within the mixture. This improves the swelling ratio and stabilizes Au NPs in networks. Furthermore, a cross-linked poly (PDMA-co-AAm-co-AAc) random hydrogel was also prepared with the same monomer compositions as the above hydrogel for comparison of their properties. Then, swelling, thermal sensitivity and thermal and optical switching properties of the prepared hydrogels were investigated in two acidic (pH=1.2) and neutral (pH=7.4) buffered solutions to simulate stomach and intestine body conditions. Finally, loading and cumulative release (%) of ofloxacin antibiotic as model drug were considered in both thermal and optical switching conditions. Based on these results,

pulsatile release vehicle was obtained which have the "on" state at higher temperatures and the "off" state at lower temperatures.

**Keywords:** Switchable drug release; Dual responsive polymer; Au nanoparticles; Laser enhanced release.

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## 1. Introduction

In recent years, stimuli-responsive polymers-also called smart polymers-which exhibit conformational changes in their network structure and swelling properties in response to one or two environmental stimuli, have been used in many applications such as drug and gene delivery [1-3], sensing [4, 5] and separation science [6-8]. Such conformational changes can be triggered by varying their environmental compositions (such as pH) [9] or thermodynamic conditions (such as temperature, an externally applied voltage or exposure to light) [10, 11] and they have the ability to return to their original shape after removing the applied trigger [12].

By now, temperature and pH were mostly stimuli used to trigger conformational changes in hydrogels [13, 14]. Using temperature as the stimulus is limited to use hydrogels with phase transition temperatures very close to the body conditions. In other word, the upper/lower critical solution temperature (UCST/LCST) of these polymers should be in the range of 32-37 ºC which limits the number of applicable thermo-responsive polymers for drug delivery [15].

Using light as the stimulus is particularly interesting because it can be applied highly localized without the need to direct contact with responsive materials [16]. Therefore, it can supply the heat necessary for phase transition to release drug. By now, most light-responsive polymers contain photo-sensitive chromophores integrated into the polymer backbone or as pendent groups [17]. Dyes can induce switching in both direction but, the process is slow and they are chemically reactive and susceptible to bleaching.

Optical switching can be also obtained by local generation of heat by metal nanoparticles [18], which are either covalently linked or simply trapped in hydrogels [19]. Unlike dyes, metal nanoparticles cannot induce switching in both directions. However, they are very stable and generated heat dissipates quickly in the environment so that cooling process can provide a

passive reverse response mechanism once the trigger is turned off [20]. In fact, nanoparticles with size dependent surface plasmon resonance (SPR) property are very interesting and gold nanoparticles (Au NPs) in particular, which are inert and biocompatible, are therefore one of the best choices for using in drug delivery systems [21]. Responsive polymers containing Au NPs have promising applications different research areas such as oncology [22], sensing and catalysis [23], semiconductors and electronic device [24], microlens [25], antimicrobial materials [26], drug delivery [17]. In fact, combination of a temperature-responsive hydrogel and SPR-based metal nanoparticles creates a dual light- and temperature-responsive switchable hydrogel which can convert light into heat through non-radiative decay of surface plasmon resonance. This can also allow using temperature-responsive polymers with LCST or UCST properties higher than body temperature and extent the number of smart polymers used for drug delivery systems.

In this research, synthesis and swelling properties of poly dimethylacrylamide-co-acrylamide P(DMA-co-AAm) as IHG, poly acrylic acid grafted IHG [(P(DMA-co-AAm)/PAAc] as SHG and Au NPs trapped in the network of SHG (Au NPs-SHG) were investigated and compared with that of random copolymer hydrogel composed of the same monomer compositions. Then, phase transition, switching properties (both thermal and optical), and drug loading and release behaviors of SHG and Au NPs-SHG were studied in two acidic and neutral buffer solution with pH=1.2 and 7.4 to simulate body conditions. Finally, ofloxacin was used as a model drug for loading and release experiments of the synthesized hydrogels to examine their capability of using as controlled drug carriers. The results reveal that the synthesized hydrogels have properties of dual light- and temperature-responsiveness and are suitable to be applied in different area such as biomedical and pharmaceutical industries.

## 2. Experimental

### 2.1 Materials

All chemicals were of analytical grade and used as received without further purification. Acrylamide (AAm), N, N'-dimethylacrylamide (DMA), acrylic acid (AAc), ammonium persulfate (APS), methylene-bis-acrylamide (MBA), hydrogen tetrachloroaureate (III) hydrate ($HAuCl_4$), sodium dihydrogen phosphate ($Na_2HPO_4$), potassium chloride, sodium hydroxide, trisodium citrate, hydrochloric acid, and methanol were purchased from Merck company (Darmstadt, Germany). Deionized water was used throughout the experiments.

### 2.2 Optical set up and instrumentation

The visible laser light was produced by a homemade 532 nm laser focused on the top of a 3.8 mL quartz cell. An objective lens was mounted in front of the laser to focus the light beam to about 5 mm diameter spot, corresponding to a measured intensity of 630 kW $cm^{-2}$. The UV-Vis spectra were carried out using an Avantes irradiance-calibrated AvaSpec3648 spectrometer (Apeldoorn, Netherlands) in the range of 200-1100 nm provided with two FC-UVIR400-1ME 400 µm optical fibers, a CUV-VAR-UV/VIS cuvette holder and an AvaLight-DH-S deuterium/halogen light source. The size and morphology of Au NPs were characterized by a CM120 Phillips transmission electron microscope (Amsterdam, Netherlands) with an accelerating voltage of 100 kV. A Metrohm (Herisau, Switzerland) 827 mV/pH meter supplied with a combined electrode was used for measuring and adjusting pH of the solutions.

### 2.3 Synthesis of colloidal Au NPs

Au NPs were prepared by Turkevich approach through controlled reduction of aqueous gold ions using trisodium citrate [27] with slight modifications. Briefly, 2 mL chloroauric acid (5 mM) was added to 45 mL deionized water in a conical flask and allowed to boil with constant magnetic stirring under reflux for 10 min. The reaction was followed by addition of 3 mL trisodium citrate (25 mM) under continuous stirring. The solution color changed immediately from almost colorless to typical deep red. The reaction was remained at the same condition for 5 min and then it was rapidly cooled to the room temperature using an ice bath. The typical TEM image (Fig. 1) of Au NPs shows that the particles were relatively uniform with a mean diameter of approximately 10±1.2 nm.

**2.4 Synthesis of IHG, SHG and Au NPs-SHG hydrogels**

The initial IHG hydrogel was synthesized by free radical polymerization using MBA as cross-linker and APS as initiator. Briefly, DMA (1.25 g) and AAm (2.15 g) were dissolved in 25 mL deionized water in a 150 mL three-necked round-bottom flask equipped with a condenser, nitrogen gas inlet and a thermometer. Then, MBA (0.15 g) and APS (0.15 g) were added under stirring and the solution was degassed by nitrogen gas for 30 min. Polymerization was performed at 70 ºC for 8 h under nitrogen atmosphere. The resulting IHG initial hydrogel was centrifuged at 2150 g for 5 min after primary decantation and re-suspended in deionized water. This procedure was repeated for five times. Then, it was immersed in deionized water for two days by changing water content every 12 h to remove un-reacted chemicals and monomers. The above hydrogel was transferred to a 150 mL round bottom flask to prepare a semi-interpenetrating polymer network (semi-IPN) as secondary hydrogel. Then, 4 mL of AAc (equal to 2.18 g) and 0.15 g of APS were added in reaction mixture. After degassing, the suspension was stirred for 5 h in 70 ºC

under nitrogen atmosphere. The resulting hydrogel (SHG) was washed using the same procedure as for IHG.

In other reaction, SHG was prepared while a solution of Au NPs (20 mL, 0.2 mM) was also added to the reaction medium along with AAc and the resulted Au NPs-SHG hydrogel was washed with the same procedure as IHG. A schematic of preparing procedure and images of bulk hydrogel system were represented in Fig. 2 and 3 respectively.

Furthermore, a co-polymer composed of poly (DMA-co-AAm-co-AAc) random hydrogel (RHG) was also synthesized for comparison. The reaction conditions and monomer compositions are the same as that of IGH.

### 2.5 Swelling measurements

The swelling behaviors of IHG, SHG and RHG hydrogels were investigated in different temperatures according to the procedure described previously [28, 29]. The gravimetric method was employed to study polymer swelling. All hydrogels were dried in a vacuum oven at 50°C for 2 days. After immersion in deionized water at a desired temperature for 2 h, the samples were removed from the solution and blotted with filter paper to remove excess water on the polymer surface and weighed. The average value of three measurements was taken for each sample and swelling ratio (SR) was calculated using $SR= (W_s - W_d)/W_d$ equation, where $W_s$ is the weight of swollen polymer and $W_d$ is the weight of dried polymer.

### 2.6 UCST measurements of hydrogels

Volume-phase transition temperature of the hydrogels was determined from the transmittance measurements of IHG, SHG and RHG in two buffered solutions (standard acidic solution;

pH=1.2, 50 mM KCl + 64 mM HCl and standard neutral solution; pH=7.4, 50 mM $Na_2HPO_4$ + NaOH) at 500 nm as a function of temperature. 3 mL of each buffered solution containing 0.15 g of each hydrogel was transferred to a quartz cell which fixed in a cell holder with a device for water circulation adjusted to the desired temperature and its transmittance was recorded in each temperature.

### 2.7 Thermal and Optical sensitivity and switching

Thermal sensitivity of SHG and Au NPs-SHG hydrogels in two different pH solutions (1.2 and 7.4) was investigated by measuring their transmittance changes as a function of temperature. A solution of 5% w of each hydrogel was used and the experiments were performed as the same procedure mentioned for UCST. Furthermore, thermal switching properties of these hydrogels were investigated in buffered solution with pH=7.4. An amount of 0.15 g of each SHG or Au NPs-SHG hydrogel was transferred into 3 mL buffer and uniformly heated for 30 s until reach 60 ºC. Then the sample was left to the ambient temperature to undergo passive cooling. Two complete heating cycles in 200 s were performed.

In the next experiments, optical switching of Au-SHG hydrogel was studied while the samples were pre-heated to the temperature of 50 ºC, very close to the UCST of SHG in buffer solutions with pH 1.2 and 7.4. Samples were illuminated for 30 s at 630 mW $cm^{-1}$ followed by passive cooling to room temperature with minimum transmittance.

### 2.8 Drug loading and release experiments

Ofloxacin loading of the hydrogels was performed based on the previously reported method [30] with slight modifications. Briefly, 0.5 g of each hydrogel (SHG or Au NPs-SHG) was transferred

to a 100 mL beaker containing 50 mL of ofloxacin solution (84 ppm) and left for 24 h. After loading, concentration of the drug in supernatant was measured spectrophotometrically at 298 nm. Appropriate dilution performed to ensure the absorbance is in linearity range of Beer's law. Then, in-vitro release studies were performed in response to temperature changes in two buffered solutions with pH 1.2 and 7.4 which were selected for release medium. Each ofloxacin loaded SHG or Au NPs-SHG was immersed into the 3 mL of each buffered solution in a quartz spectrophotometric cell. The cell was put into two water baths with fixed temperature at 35 and 55 ºC and mutually transported between two baths to change the temperature of cell. At predetermined time intervals, upper solution was analyzed spectrophotometrically to determine the cumulative drug released.

**3. Results and Discussion**

The aim of this study was to prepare a hydrogel with a positive temperature-dependent swelling change using a pair of polymers which show attractive intermolecular polymer-polymer interactions, specifically, complex formation by hydrogen bonding. The complex formation/dissociation in the synthesized hydrogel can be expected to cause reversible shrinking/swelling changes with respect to temperature change. To synthesize such a hydrogel, a semi-IPN composed of P(DMA-co-AAm) and PAAc blocks were used. It can more effectively preserve rapid kinetic response rates to temperature due to the absence of a restricting interpenetrating elastic network (due to the absence of second cross-linker) while still providing slow drug release. Furthermore, the blocks can form intermolecular complexes by hydrogen bonding at lower temperature and dissolve at higher temperature because of complex

dissociation. Volume-phase transition temperature of such a synthesized hydrogel depends on the stability of intermolecular complexes.

On the other hand, temperature sensing of the prepared hydrogel should be enough for drug delivery applications. For this reason, we put SPR-based Au NPs in the structure of the synthesized hydrogel. In this manner, Au NPs were added in the second step of synthesis procedure. In fact, active -NH and -OH functional groups in polymer network act as head groups to adsorb and stabilize Au NPs. These particles absorb specific wavelength of light and convert it to heat. So, the vehicle could have switching ability with respect to light radiation.

### 3.1 Swelling measurements

Temperature dependence of swelling ratio in deionized water for IHG, SHG and RHG hydrogels is shown in Fig. 4. As can be seen, all hydrogels show positive swelling changes with increasing temperature. In fact, low swelling ratio of the hydrogels at lower temperatures is due to the insolubility of polymeric chains which is as a result of hydrogen-bonding formation between AAc part with the other two monomers and increasing in swelling ratios with increasing temperature presumably results from the dissociation of these hydrogen bondings. Indeed, it seems that when the temperature is low, the building block of the hydrogel can form continuous ladder-like interactions [31] composed of many DMA-AAc and AAm-AAc units. Formation of this ladder-like complex probably causes shrinkage observation in low temperatures and when the temperature increases, some complex units may start to dissociate by dissociation of hydrogen bondings and this dissociation which are involved with broken units can promote the cooperative dissociation of adjacent complexes because of strong hydration forces.

As can be seen from Fig. 4, swelling ratio of SHG is close to that of its respective initial gel in lower temperatures, while higher swelling ratios are observed at higher temperatures. On the other hand, since DMA, AAm and AAc units are polymerized randomly in RHG, continuous sequences of these monomers might be difficult to form, Subsequent DMA-AAc and AAm-AAc complexes are liable to be dispersed in small clusters in isolated states within the polymeric matrices and dissociation of certain complex units possibly do not affect other bonding sections. For this reason, RHG hydrogel shows gradual and exponential swelling changes with temperature change.

### 3.2 UCST measurements of hydrogels

Volume-phase transition temperature of the three hydrogels was studied at two different pH solutions. Fig. 5a represents the UCST of IHG, SHG and RHG hydrogels at pH=1.2. As reported in the literature, the $pK_a$ value of AAc monomer is 4.2 [29]. In pH value much lower than the $pK_a$, almost all carboxylic acid groups in the polymer are in the form of COOH. Thus, the polymer is neutral and the hydrogen bonds between -COOH in AAc with together and with carbonyl groups in AAm and DMA moieties led to strong polymer-polymer interactions and complexaction. As a result, the flexibility of the polymeric chain and therefore, swelling ratio of the hydrogels is relatively low and collapsing is followed by aggregation of hydrogel particles.

All hydrogels network undergoes a volume phase transition from shrunken to swollen state by increasing temperature. The driving force for this temperature-sensitive volume-phase transition was considered to be a balance between hydrophobic/hydrophilic interactions between network chains and water molecules. As mentioned, there is a greater degree of hydrogen bonding between monomer units of polymer chains at low temperature. Upon increasing the temperature,

these attraction forces become weak and hydration occurred in the polymer network leading to the swelling.

Fig. 5b shows the temperature dependence of transmittance for the three hydrogels at pH=7.4. Together with the results for pH=1.2, a pH-induced volume change is clearly observed at all temperatures and increasing in initial transmittance and broadening of the phase transition region is the characteristic of pH=7.4. At this pH, all carboxylic acid functional groups of AAc are totally ionized. The repulsive forces between the same charged groups cause hydrogels swelling. As can be seen from the figure, in higher pH temperature sensitivity of hydrogels decreases and pH effect becomes dominant.

**3.3 Thermal sensitivity**

The results for temperature sensitivity of SHG and Au-SHG at two different pHs were shown in Fig. 6. Although, the presence of Au NPs can disrupt some electrostatic integrations and hydrogen bondings between the monomers, as mentioned before, the nanoparticles were trapped in hydrogel by electrostatic interactions with monomers functional groups which cause strong complexation of Au NPs with monomer moieties [32, 33]. These interactions influence the ability of polymer chains to not swell freely at low temperatures, results in shrinkage of Au-SHG.

The volume-phase transition temperature of Au-SHG also undergoes a slight decrease in pH=1.2 due to the presence of Au NPs as compared to plain SHG (Fig. 6a) and the obtained results also reveal that transition from shrinkage to swollen state become somewhat broader and less prominent due to the incorporation of Au NPs in the SHG network which can be due to the partial charge compensation inside the polymer network due to the incorporation of

nanoparticles. On the other hand, there is no very sharp increase in pH=7.4 which may be due to the weaker polymer-polymer and nanoparticles-polymer interactions which occur at high pHs.

### 3.4Thermal and Optical switching

The thermal and optical switching of SHG and Au-SHG hydrogels were also studied pH=7.4. For thermal switching, light transmittance was recorded for two complete cycles. As can be seen in Fig. 7, the phase transition starts immediately after heating and reaches maximum in about 16-17s. Both the SHG and Au NPs-SHG hydrogels have fast and reversible thermal switching. But, they have different phase-back times. Indeed, Au-SHG hydrogel requires about 1.5 times longer than SHG to fully collapse after turning off the heat. This could be due to a heat conductance of metal nanoparticles and difference in the re-adhesion capability of polymer above the UCST.

Fig. 8 shows the optical switching properties of SHG and Au NPs-SHG which can obtain by applying temperature achieved indirectly through local heating of the metal nanoparticles by irradiation at the SPR wavelength. On and off exposure times are indicated by solid lines. As can be seen, phase transition for Au NPs-SHG begins quickly (after about two second) and it reaches highest transparency at about 17 s while, SHG shows small changes in transmittance when expose to the light.

As mentioned before, the mechanism of optical switching for Au NPs-SHG relies on the energy conversion of the light absorbed by the Au NPs at the SPR, which is energetically lower than the lowest inter-band transition of gold at around 470 nm [34]. So, SPR energy absorbed by nanoparticles dissipated as heat to the surrounding environment and temperature-responsive hydrogel around these NPs get the heat. The results indicate the suitability of this hydrogel for applying in pharmaceutical industries.

### 3.5 Drug loading and release experiments

Release studies of ofloxacin from both hydrogels were investigated as a function of temperature in two different pHs. As the results revealed, the release amount of entrapped drug reflects the matrix swelling/shrinkage due to the change in both pH and temperature. In the first experiments, release of ofloxacin from SHG was studied in response to temperature changes between 35 and 55 ºC (i.e. below and above the UCST). As can be seen from Fig. 9a, for buffered medium with pH=1.2, some drug release was happen even below the UCST. At this pH, the hydrogel collapse and deswelling, with respect to loading situation, can promote ofloxacin release to some extent. For this reason, an increase in release (%) with gentle slope can be observed in each lower temperature too. But, the phenomenon will fade out as the time increases. For pH=7.4(Fig. 9b), the hydrogel is in its swelling state at the beginning. Therefore, the only motivation for further release is temperature rise. In each temperature-raising step, release rate was sharply increases for both pHs as expected.

The results for optical-driven release of Au NPs-SHG were presented in Fig. 10. For each radiation step, laser beam was radiated about 15s right after 10, 25 and 40 min after the beginning of release experiments. As can be seen, primary increase in release amount was also observed in pH=1.2. As a consequence, the slope of drug release after light radiation is found to be lower in this pH. On the contrary, this slope is very sharper for the hydrogel at pH=7.4. This makes Au NPs-SHG hydrogel a suitable candidate as a carrying vehicle for controlled drug release.

## 4. Conclusion

In this research, plain [P(DMA-co-AAm)/PAAc] hydrogel as SHG with a positive temperature dependent swelling change was synthesized using a pair of polymers which show attractive intermolecular polymer-polymer interactions, specially complex formation by hydrogen bonding. In another experiments, synthesized Au NPs were attached inside the SHG network to form a stable and opto-thermally responsive hydrogel. Immobilization of Au NPs throughout the hydrogel networks, not only on the surface but also inside the networks, was due to the complexation of Au with functional groups in polymer chains. The swelling properties of synthesized hydrogels in deionized water and temperature sensitivity of SHG and Au NPs-SHG hydrogels in acidic and neutral pH (simulation of stomach and intestine conditions) were investigated. Furthermore, thermal and optical switching properties of both plain and Au NPs grafted hydrogels were also studied. The results revealed that the synthesized Au NPs-SHG can be reversibly collapsed and re-suspended with fast response times in the order of few seconds by heat and light at the surface plasmon resonance wavelength of attached NPs. Finally, loading and release of ofloxacin from the hydrogels in different temperature and two pH conditions were considered. The results revealed that these smart hydrogels with switchable on/off release properties may find important applications in pharmaceutical and biomedical industries.

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**Figure captions:**

Fig. 1 TEM image of the prepared Au NPs.

Fig. 2 Schematic of preparing procedure for the composite.

Fig. 3 Images of bulk hydrogel system for a) SHG and b) Au NPs-SHG.

Fig. 4 Swelling behaviors of IHG, SHG and RHG in deionized water in different temperature.

Fig. 5 Volume-phase transition temperature of hydrogels at a) pH=1.2 and b) pH=7.4.

Fig. 6 Thermal sensitivity of SHG and Au NPs-SHG at a) pH=1.2 and b) pH=7.4.

Fig. 7 Thermal switching of SHG and Au NPs-SHG at pH=7.4.

Fig. 8 Optical switching of SHG and Au NPs-SHG at pH=7.4.

Fig. 9 Results for release (%) of ofloxacin for SHG at a) pH=1.2 and b) pH=7.4.

Fig. 10 Results for release (%) of ofloxacin for Au NPs-SHG at a) pH=1.2 and b) pH=7.4.

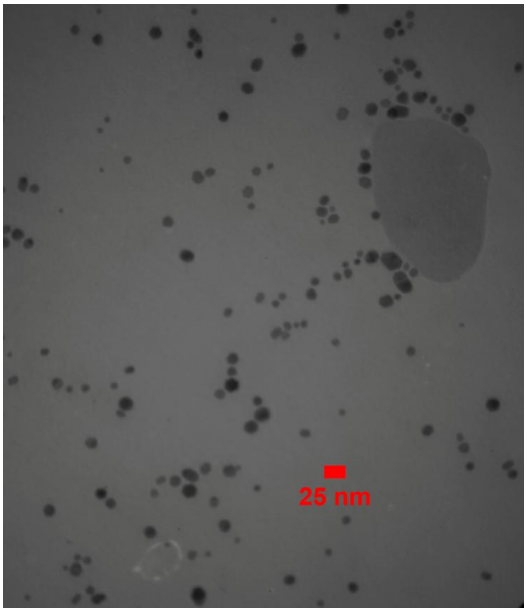
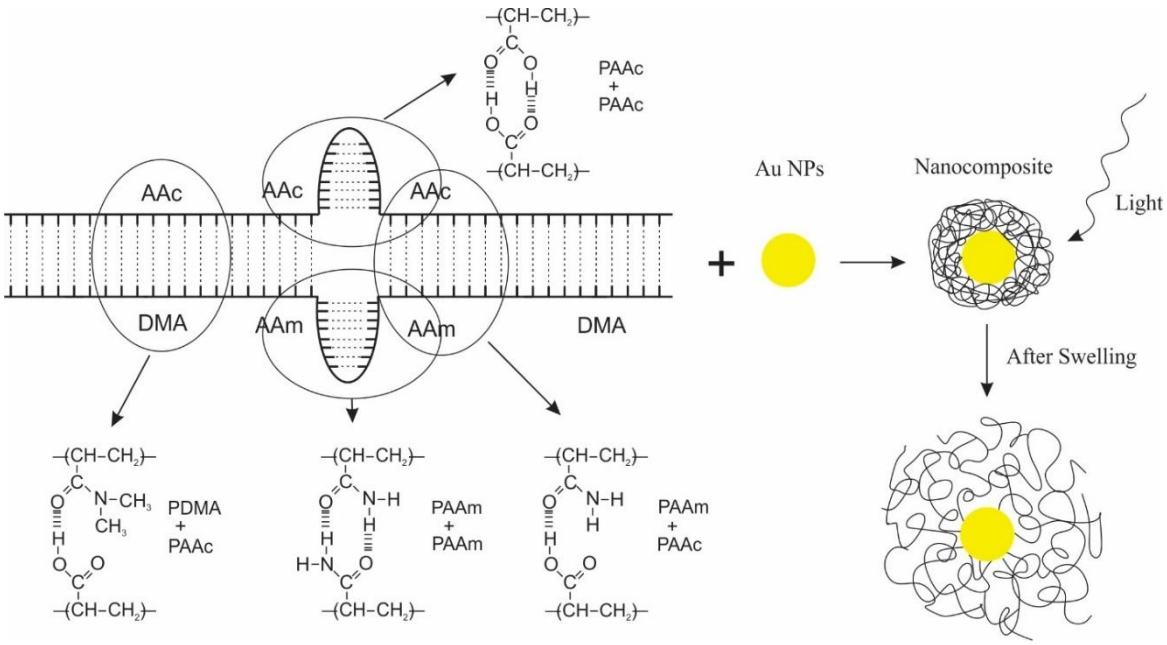



Fig. 1


AAc
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Au NPs
Nanocomposite
Light
After Swelling

Fig. 2

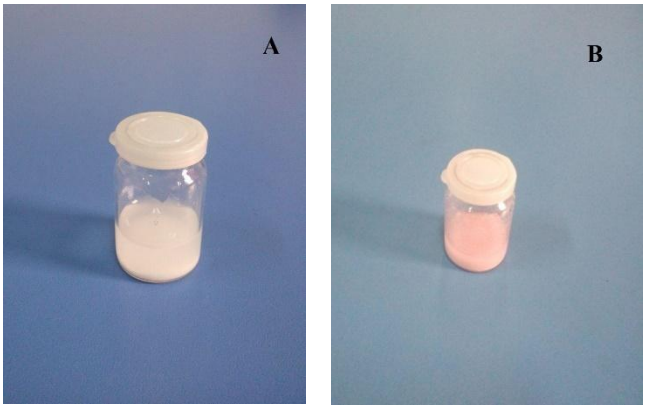



Fig. 3

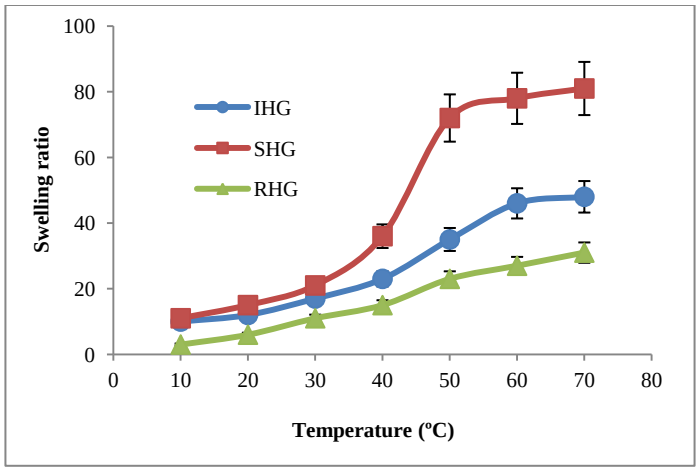
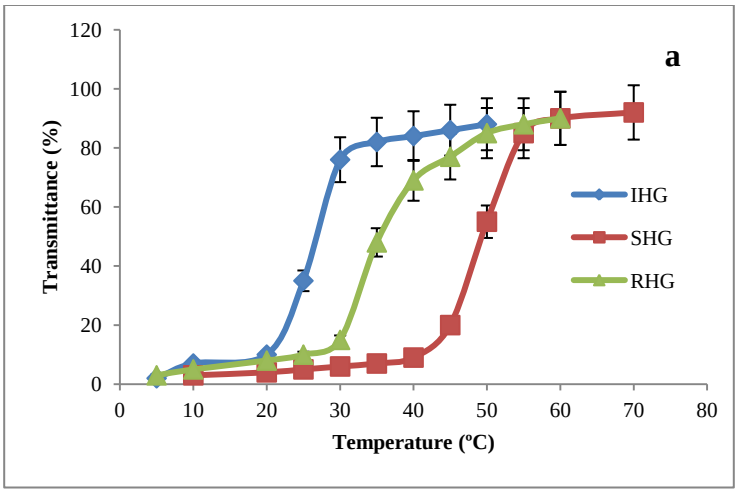

100
80
60
40
20
0
Swelling ratio
IHG
SHG
RHG
0
10
20
30
40
50
60
70
80
Temperature (°C)

Fig. 4


a
Transmittance (%)
Temperature (ºC)
IHG
SHG
RHG
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40
60
80
100
120
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30
40
50
60
70
80

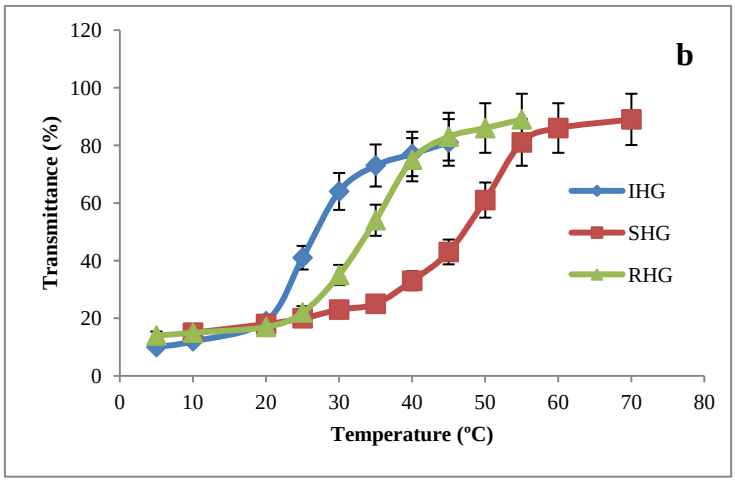
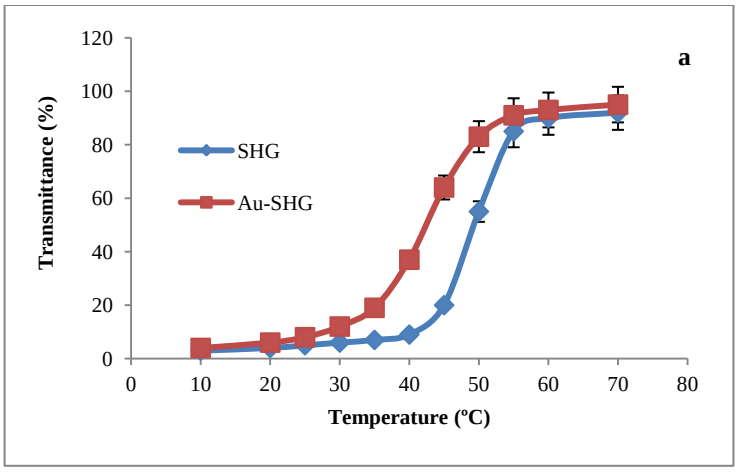

b
Transmittance (%)
Temperature (ºC)
IHG
SHG
RHG
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80

Fig. 5


a
Transmittance (%)
Temperature (ºC)
SHG
Au-SHG
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80

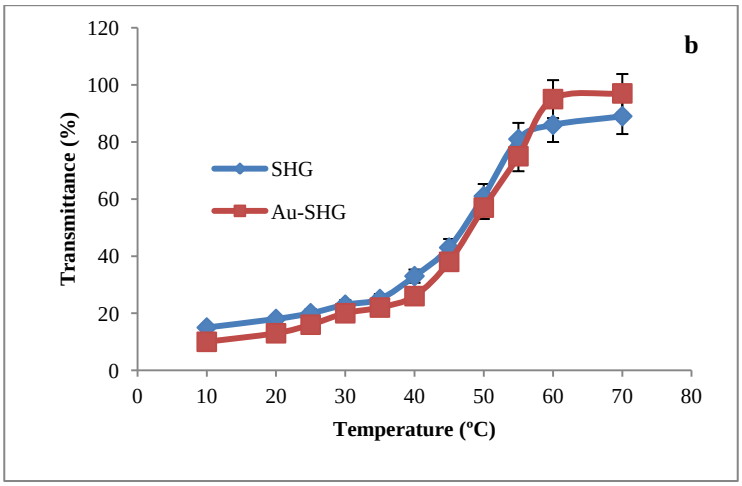

b
Transmittance (%)
Temperature (ºC)
SHG
Au-SHG
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80

Fig. 6

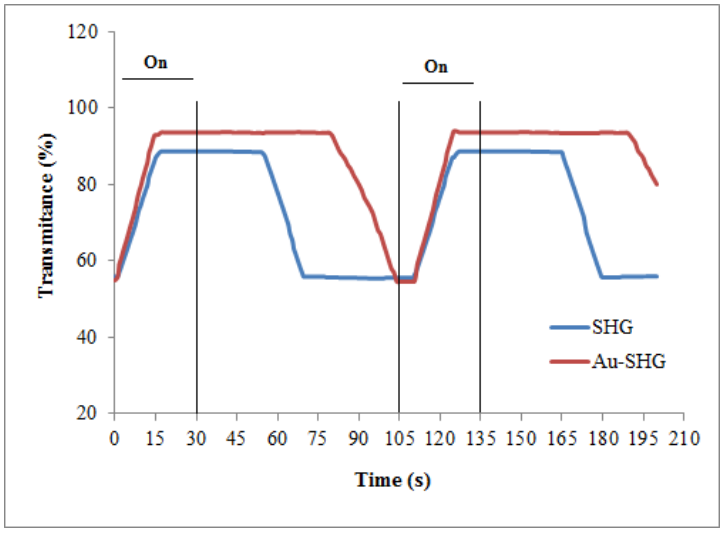

120
100
80
60
40
20
On
On
Transmitance (%)
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210
Time (s)
SHG
Au-SHG

Fig. 7

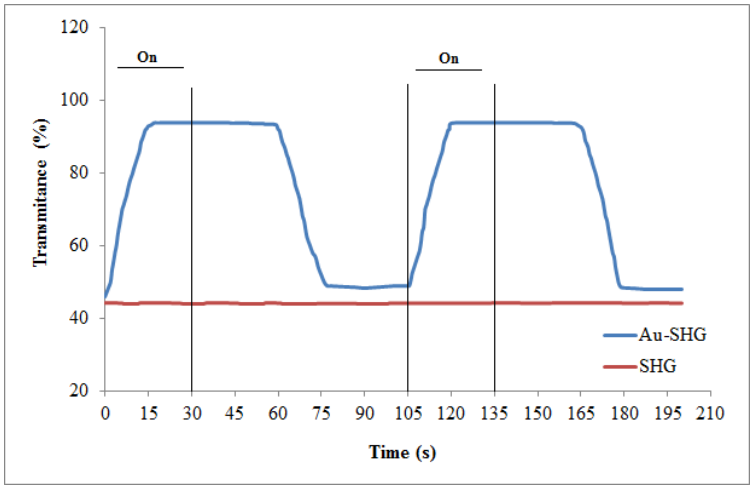
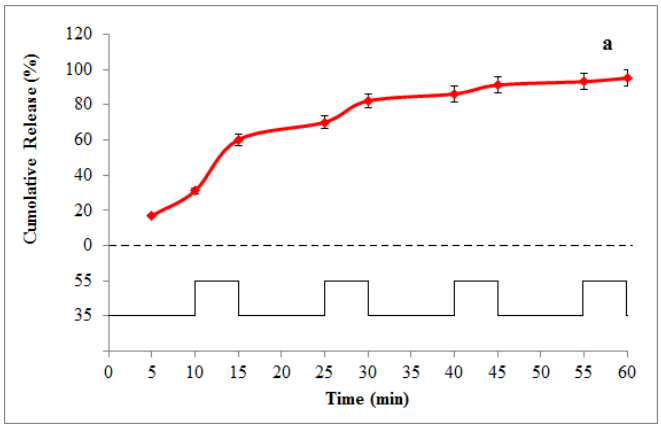

On
On
Transmitance (%)
120
100
80
60
40
20
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
Time (s)
Au-SHG
SHG

Fig. 8


a
Cumolative Release (%)
120
100
80
60
40
20
0
55
35
0 5 10 15 20 25 30 35 40 45 50 55 60
Time (min)

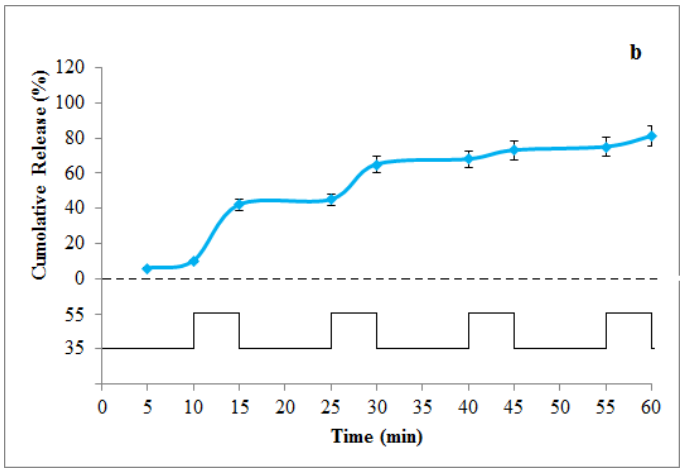

b
Cumolative Release (%)
120
100
80
60
40
20
0
55
35
0 5 10 15 20 25 30 35 40 45 50 55 60
Time (min)

Fig. 9

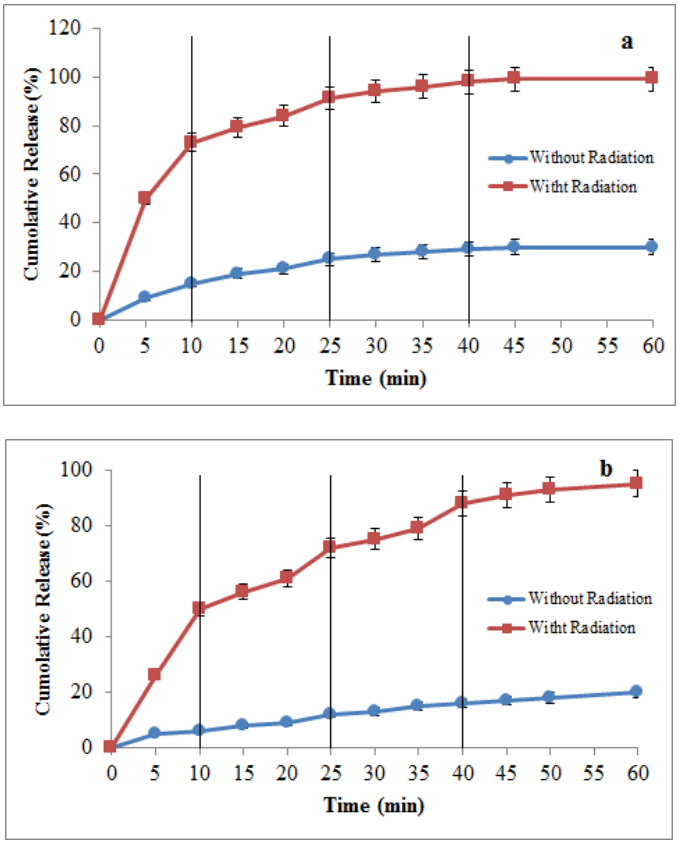

a
Cumolative Release (%)
Time (min)
Without Radiation
Witht Radiation
b
Cumolative Release (%)
Time (min)
Without Radiation
Witht Radiation

Fig. 10