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Preparation and properties of different photoresponsive hydrogels modulated with UV and visible light irradiation

Jianwei Liu, Jun Nie, Yufei Zhao, Yong He*

State Key Laboratory of Chemical Resource Engineering and Key Laboratory of Carbon Fiber and Functional Polymers, Ministry of Education, Beijing University of Chemical Technology, Beijing 100029, PR China

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ABSTRACT

Two different types of hydrogel containing azo group were designed and prepared via UV and visible light initiating photopolymerization technology respectively. The obtained two hydrogel showed different swelling properties and control release behaviors with Ribavirin as model drugs. Upon additional irradiation, they exhibited different photo response characters, which may be due to the different isomer states of azo group under different light irradiations and the interior morphology of hydrogel investigated by scanning electron microscopy (SEM).

1. Introduction

Over the last several decades, the environment sensitive hydrogel had attracted extensive interest for their potential application to the biomedical areas such as drug deliverers and tissue engineering scaffolds. Responsive hydrogel were able to undergo large chain conformational changes with respond to slight environmental stimuli such as temperature [1–4], pH [4–7], light [8,9], glucose [10], electric signal [11], pressure [12], and so on [13].

Among these intelligent hydrogel, pH-sensitive hydrogel were limited by hydrogen ion diffusion, while temperature sensitive hydrogel were constricted by thermal diffusion and temperature increasing had adverse consequences for some target molecules. Since light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogel may possess special advantages over others. Several successful examples had been reported on photoresponsive gels. Watanabe et al. [14] utilized a comonomer solution containing acryloyacetone, acrylamide, and *N*,*N*′-methylene bisacrylamide to produce photoresponsive hydrogel cantilever, which can deflect under illumination. Mamada et al. [15] reported the observation of the photoinduced phase transitions of gels by introducing a leuco derivative molecule into the polymer network, and determined one as a function of temperature under UV irradiation. Kuang et al. [16] synthesized an amino acid based dendron photoresponsive organogel, which showed gel–sol or sol–gel transition with irradiation UV light at 365 nm or 254 nm respectively. Sugiura and co-workers [17] presented the application of photoresponsive polymer gel microvalves, which was controlled by local light irradiation with blue light.

Photoresponsive hydrogel containing azobenzene chromosome was the most representative intelligent hydrogel, which can expand or contract due to photoinduced structural deformation resulting from azo group. Upon irradiation, azo group occurred to trans–cis isomerization and exhibited large change in size, shape or polarity. Patnaik et al. [18] synthesized a kind of photoresponsive azo-dextran polymer, which could act as a nanogel drug carrier. Chen et al. [19] studied the good pH responses and photoresponses of hydrogel composed of acrylamido azo and acrylic acid. Tomatsu et al. [20] investigated the viscoelastic properties and the effect of the length of the alkyl chain connecting the main chain and the azo moiety. Sakai et al. [21] had developed a new type of photoresponsive polymer gels by introducing an azobenzene moiety on the mobile cyclodextrin part as the sliding cross-linking unit. They infer that the large photoinduced deformation for photoresponsive polymer gels and appearance of transient overshooting behavior in the swelling process are due to the pulley effect of the mobile cross-linkers.

The above hydrogel were all synthesized via thermal polymerization technology. But photopolymerization technology is more suitable to prepare bio hydrogel due to its moderate reaction condition, fast rate and space modulate ability [22,23]. On the other

* Corresponding author. Tel.: +86 1064421310.
E-mail address: heyong@mail.buct.edu.cn (Y. He).

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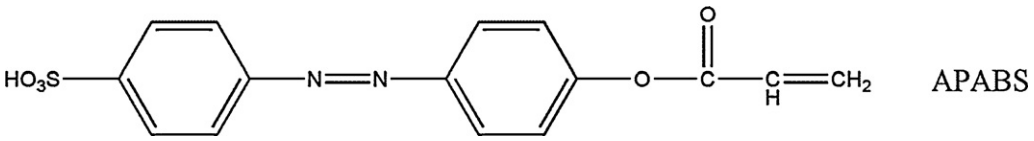


Scheme 1. Molecule structure of APABS.

hand, many photoresponsive functional groups could be modulated to specific state by the light at the same time with photopolymerization. So the obtained hydrogel should be diverse under varying light irradiated due to different isomer populations. In this paper, a water-soluble azo monomer with fast photoresponse time was synthesized and two kinds of photoresponsive hydrogel were prepared via photopolymerization technology with either UV or visible light. FTIR, UV–vis spectroscopy, SEM, swelling ratio and drug release were investigated for the obtained hydrogel.

2. Materials and method

2.1. Materials

Acryloyl chloride was purchased from Beijing Sanshengtengda Technology Co. Ltd. Visible photoinitiator camphorquinone (CQ) and coinitiator ethyl 4-*N*,*N*-dimethylaminobenzoate (EDMAB) was purchased from Aldrich. *N*,*N*-Methylene bisacrylamide (MBAA, Tianjin Fuchen Chemicals Reagent Factory) was purified by recrystallization from methanol. UV photoinitiator 2,4,6-trimethyl benzoyldiphenyl phosphine oxide (TPO) was obtained from Polynaisse Resources Chemical Co. Ltd. (Shanghai, China) and used as received. Hydroxyethyl acrylate (HEA) was purchased from Beijing Chemical Reagent Company. Polyethylene Glycol(600) Diacrylate (PEGDA-600) was kindly supplied by Sartomer Company Inc. (USA). Other reagents and solvents were purchased from Beijing Chemical Reagent Company and used without further purification. Ribavirin was kindly donated by Star Lake Bioscience Co. (Guangzhou, China). The solvents used in spectral test were of chromatographically pure reagent grade.

4-[(4-Acryloyloxy) phenylazo] benzenesulfonic acid (APABS, illustrated in Scheme 1) was synthesized through similar process and described elsewhere [24].

2.2. Instruments

The UV–vis spectra were obtained by using Hitachi 3010 spectrophotometer, and the air-tight screw-capped cells with 1 cm path length were employed. The ultraviolet (UV) light irradiated to the azo compound solution was from 100 W Hg arc lamp passed through EXFO filter assay (320–390 nm) and visible light was from 500 W xenon (CHF-XM-500W, Changtuo Technology Co. Ltd.) lamp passed through another EXFO filter assay (400–500 nm). SEM images were taken on a scanning electron microscope at an accelerating voltage of 10 kV (Hitachi S-4700, Hitachi Co.). Before observation, the samples should been fixed on stubs with sputter coated with gold.

2.3. Photoisomerization investigation of APABS

The solution of APABS (1.144×10^{-4} mol dm^{-3}) in dimethyl sulfoxide (DMSO) was bubbled 40 min with N_2 and then irradiated with different wavelength light respectively. UV–vis spectra were recorded with different irradiation time intervals from 2 s to 4 s on Hitachi 3010 spectrophotometer.

2.4. Preparation of azo-hydrogel by photopolymerization with different light irradiations

The cis-hydrogel and trans-hydrogel were prepared via photopolymerization technology with different light irradiations. Various composition precursor solutions, as shown in Table 1, were placed in a mold made from glass slide and spacers with 10 ± 1 mm in diameter and 1 ± 0.2 mm in thickness, and irradiated by UV or visible light (80 mW/cm^2) for 30 min. The resultant hydrogel were washed with distilled water 5 times to remove monomers and initiator. The hydrogel were stored at room temperature in the dark.

2.5. The interior morphology of hydrogel

The samples were taken out from the models, and then quickly frozen by liquid nitrogen. The samples were freeze-dried in a freeze-drier under vacuum at −50 °C for 24 h, and were fractured carefully in liquid nitrogen. Morphology of sample was observed by scanning electron microscope (SEM).

2.6. Swelling kinetics of hydrogel

The dried hydrogel (obtained by vacuumed oven for 48 h at 40 °C) with various compositions were immersed into the buffer solutions of pH 7.6, which were prepared by adding appropriate quantities of disodium orthophosphate and citric acid to distilled water. At designed time points, the swollen gels were pulled out from the buffer solutions and weighted after removing the excess water on the surface with filter paper.

Table 1
Composition of different hydrogels.

Sample code	UV light					Visible light				
	C0	C1	C2	C3	C4	T0	T1	T2	T3	T4
HEA (g)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
PEGDA-600 (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
MBAA (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
TPO (g)	0.1	0.1	0.1	0.1	0.1					
CQ (g)						0.1	0.1	0.1	0.1	0.1
EDMAB (g)						0.1	0.1	0.1	0.1	0.1
APABS (g)	0	0.02	0.04	0.06	0.08	0	0.02	0.04	0.06	0.08
H_2O (mL)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

HEA: hydroxyethyl acrylate; CQ: camphorquinone; PEGDA-600: Polyethylene Glycol(600) Diacrylate; MBAA: *N*,*N*-methylene bisacrylamide; TPO: 2,4,6-trimethyl benzoyldiphenyl phosphine oxide; EDMAB: ethyl 4-*N*,*N*-dimethylaminobenzoate; APABS: 4-[(4-acryloyloxy) phenylazo] benzenesulfonic acid.

The equilibrium swelling ratio (SR) was defined as follows:

$$SR = \frac{W_t - W_0}{W_0} \times 100\%$$

where W_0 and W_t were the weights of the dried gel and swollen hydrogel at time t.

2.7. Release behaviors of hydrogel

The dried hydrogel were immerged into the 2 mL Ribavirin solution (0.05 wt%) for 2 days at room temperature. After equilibrated, the gels disks were taken out and put into conical flasks containing 100 mL buffer solutions (pH 7.6). The release of drug content was measured at predetermined times from 1 min to 60 min until reached constant. After that, the sample and 2 mL buffer solutions were taken out into another 10 mL beaker and irradiated for 10 min with UV or visible light. After reached designed time, the hydrogel with 2 mL solution was moved back into conical flasks and mixed evenly, and then 2 mL solution of it was pipette out to measure the released behaviors. The release of Ribavirin was determined using a calibration curve at the wavelength of 207 nm by UV–vis spectrophotometer.

The relative release ratio was defined as follows:

$$\text{relative release ratio} = \frac{W_r - W_s}{W_s} \times 100\%$$

where W_r and W_s were the weights of drugs release at time r after irradiation and at the stationary stage before irradiation respectively.

3. Results and discussion

3.1. Spectroscopic characterization and photo isomerization of monomer

As shown in Fig. 1, there is an absorption peak at 326 nm for APABS, which could be assigned to the π–π* transition of trans isomer. When exposed to the UV light, this absorption peak intensity showed obvious decline due to the trans–cis isomerization. The intensity of absorption peak at 430 nm corresponding to the n–π* transition of cis isomer inclined at same time. But when visible light was applied to above reacted system, the back isomerization from cis to trans state could be observed with high repeatability. However, this photo isomerization phenomenon should be obstructed when APABS was copolymerized with HEA and MBAA due to confining of the polymer network.

3.2. Interior morphology of hydrogel

The hydrogel photopolymerized with UV light were coded as C0–C4, while irradiated with visible light were T0–T4. Due to photoisomerization of azo group, the hydrogel of C0–C4 kept cis state, but hydrogel of T0–T4 kept trans state, mostly.

Incorporation of APABS into hydrogel could change the hydrogel microstructures as illustrated in Fig. 2, which showed the interior morphology of hydrogel. It was clear that there was no pores in the C0 and T0, while the irregular pores in the networks formed could be seen in the others. That implied there was a direct relationship between azo group and pores formation. On the other hand, C0 and T0, with same composition and different initiator and light sources, had same microstructure, which proved that the formation of pore was not affected by the initiator and light sources. The series of T1 → T4 hydrogel exhibited more and larger pores than series of C1 → C4, which was probably attributed to the different isomers state population of azo group in two hydrogel. Especially in cis-hydrogel, some of less stable cis configuration occurred cis–trans

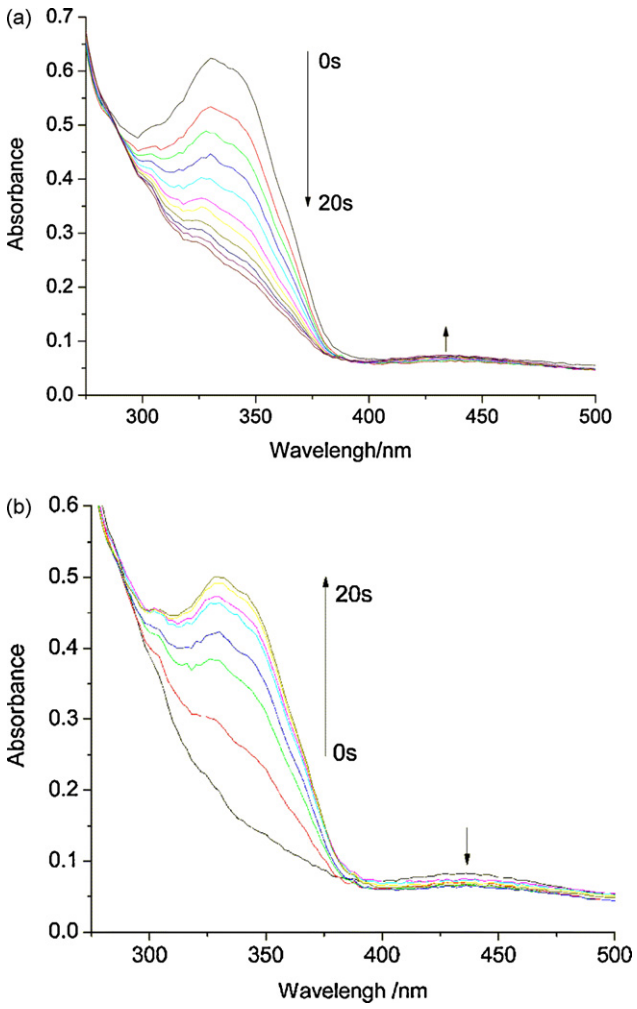


Fig. 1. Photoisomerization of APABS in DMSO (a) upon UV irradiation (320–390 nm) and (b) upon visible irradiation (400–500 nm) after UV irradiation, [APABS]: 1.144×10^{-4} mol dm^{-3}.

isomerization through thermal relaxation, so the hydrophilic and compatibility of polymer changed and caused significant change in its size and shape. This character of the hydrogel was very valuable to the loading and releasing of drugs.

3.3. Swelling kinetics of hydrogel

Swelling kinetics is one of the most important properties for control released hydrogel. The swelling ratio of produced hydrogel before and after further irradiation was measured. It could be seen that after equilibrium swelling ratio of T0 → T4 and C0 → C4 reached constant, two kinds of gels showed varying degrees of photoresponsive behavior with UV light and visible light irradiation respectively.

As seen in Fig. 3, SR of all photoresponsive hydrogel increased with prolonged time and reached equilibrium finally after 120 min. Before light irradiation, the SR property of hydrogel is controlled by the internal structure and hydrophilic of the gel. But under the light irradiation, the changing trend correlated with the content of azobenzene and their isomeric states in the hydrogel. After SR reached constant, with the different light irradiations, swelling ratio of photoresponsive hydrogel were all declined obviously except T0 and C0. These two systems were little affected by the light irradiation, which may be due to tiny thermal effect of light. However, this could be negligible compared to the change

of others caused by light irradiation. As the content of APABS in the copolymer gel increases, the equilibrium swelling ratio of trans-hydrogel decreases, which was attributed to the fact that the ionized conferred sufficient hydrophilicity to the hydrogel. For the loose structure of the series of T1 → T4, the cis → trans photoisomerization caused the decrease of volume of polymer, which resulted in the more pores forming, and then excess water was easily flowed out (Scheme 2). While the series of C1 → C4, as the

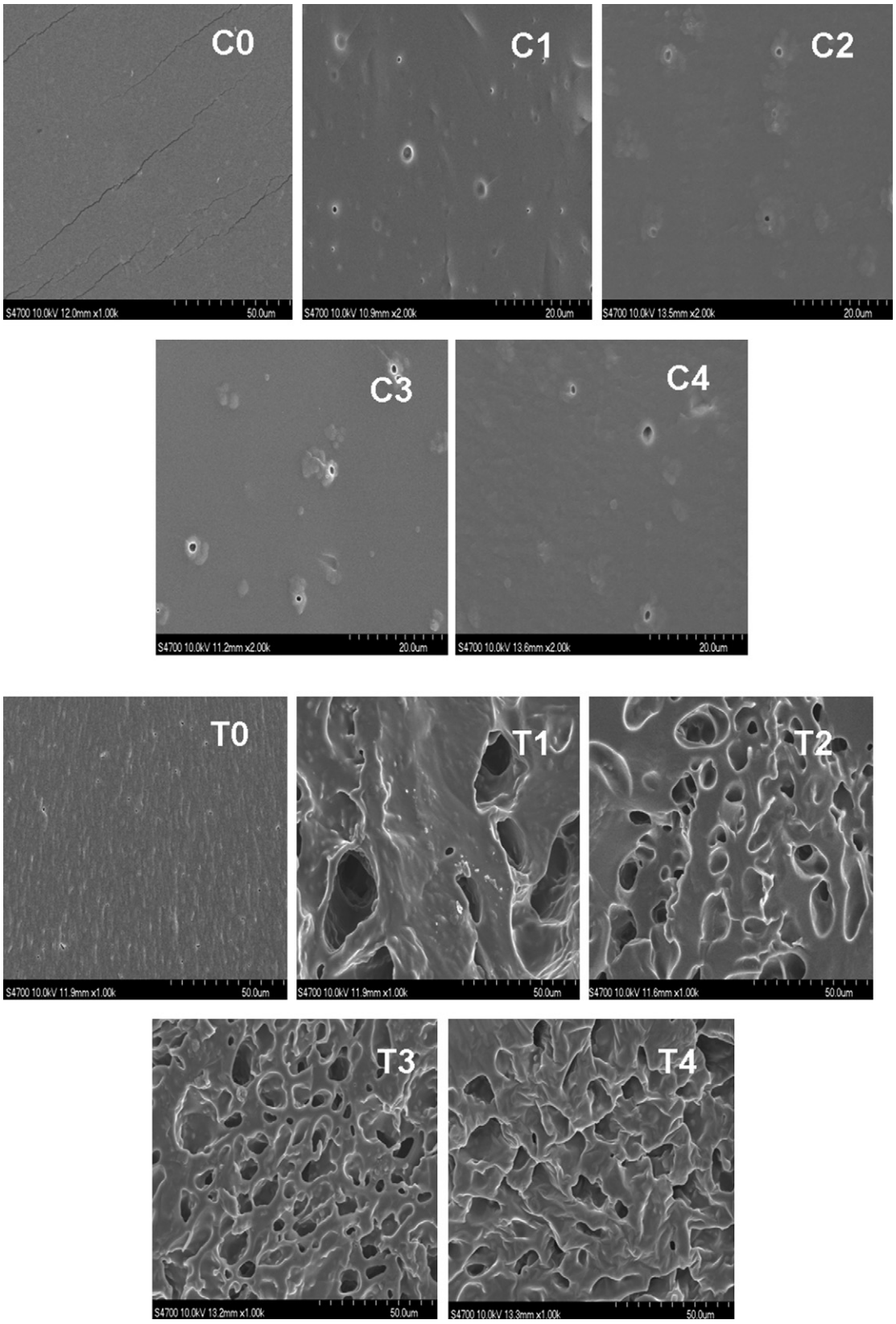


Fig. 2. SEM images of various compositions hydrogel.

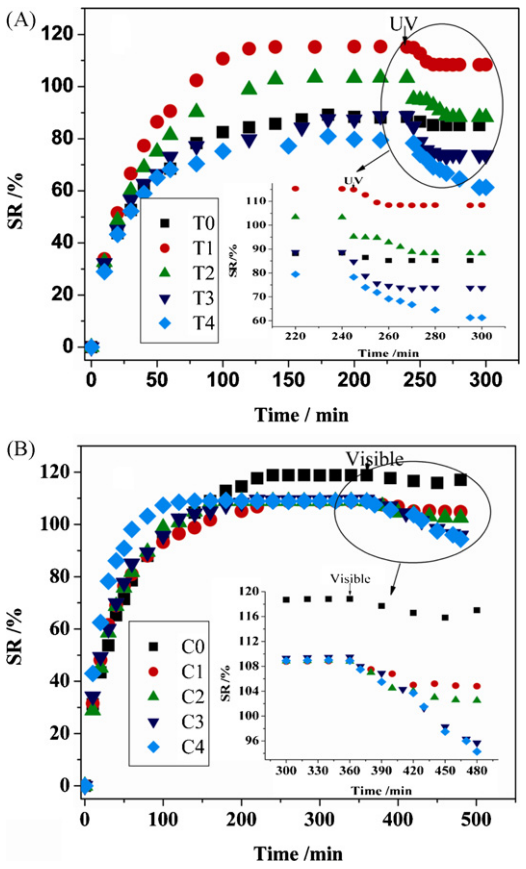
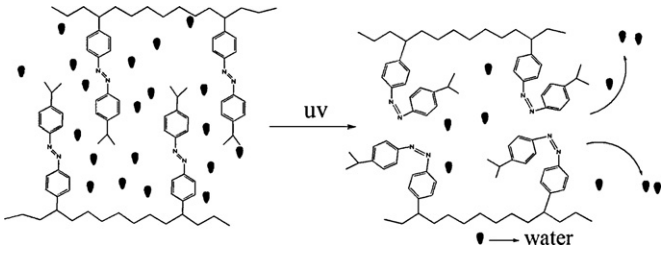
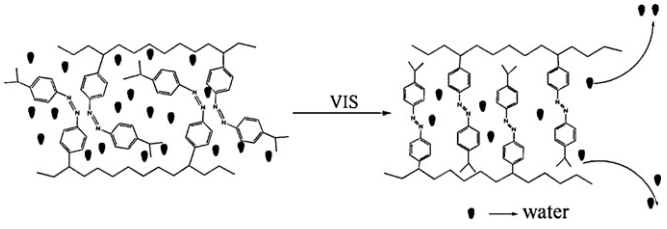


Fig. 3. Swelling kinetics of various compositions hydrogel. (A) trans-hydrogel, (B) cis-hydrogel.

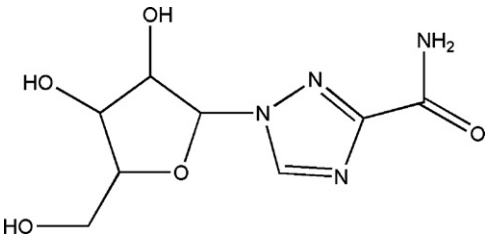
internal structure of cis-hydrogel was basically similar, the equilibrium swelling ratio and swelling rate were the same. Due to dense structure of gels, the overall volume of hydrogel remained basically unchanged, excess water was extruded following photoisomerization from trans state to cis state (Scheme 3). Because of thermal relaxation and dense structure, part of unstable cis state converted to stable trans state. Compared the two kinds of photoresponse hydrogel, T1 → T4 were more sensitive to light than C1 → C4.



Scheme 2. Swelling mechanism of trans-hydrogel.



Scheme 3. Swelling mechanism of cis-hydrogel.



Scheme 4. Molecule structure of Ribavirin.

Generally, the permeability of hydrogel depends on factors such as the pore size of the hydrogel, the types of polar groups, and interactions between polar groups and solvents, in which the dominant factor would determine the permeability properties of hydrogel. In this work, pore size was dominant factor, which corresponded to the extent of swelling of the hydrogel, and SEM was also powerful proof for this point. By changing the content of azo group or irradiation light, it was possible to adjust the pore size or porosity of networks and consequently control the rates of swelling and release of drugs.

3.4. Drug release studies

Ribavirin was selected as controlled release model drugs and its molecule structure was shown in Scheme 4. Ribavirin was a commonly antiviral drug for the treatment of epidemic hemorrhagic fever, shingles, and influenza A viral hepatitis. As a water-soluble drug bearing hydroxyl and amino groups, it might bond to APABS due to the interaction with sulfonic acid group.

The cumulative release of Ribavirin was detected by using a standard equation of curves ($y = 0.08024 + 45.74878x$, $R^2 = 0.999$)

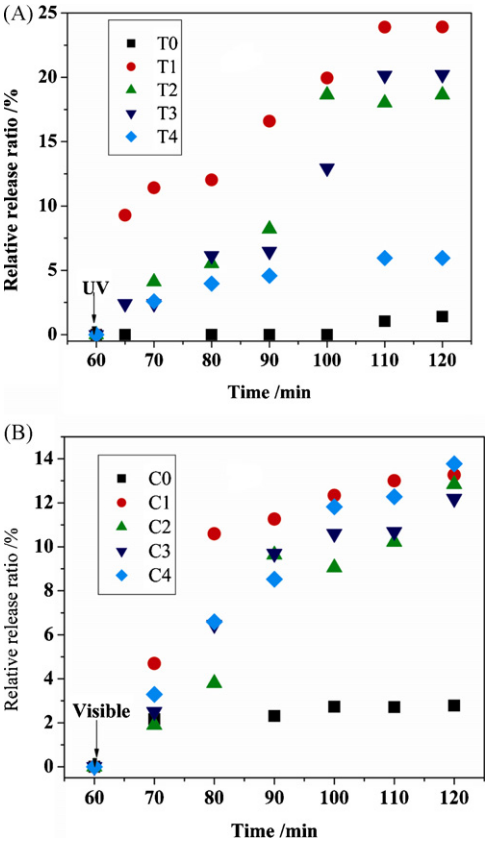


Fig. 4. Drug release of various compositions hydrogel after irradiation. (A) trans-hydrogel, (B) cis-hydrogel.

with UV–vis spectrophotometer. This assay had been reported to be fairly accurate in determining Ribavirin quantities of 2–25 μg.

As shown in Fig. 4, the drugs release of T1 → T4 was faster than that of the series of C1 → C4 under similar experimental conditions, which was consistent with its large pore size. As depicted in Fig. 4(A), after 60 min continuous release, the cumulative release of Ribavirin was kept constant. Then with UV light irradiation, the internal structures of the trans-hydrogel changed by the light at the same time with photoisomerization of azo group. When the configuration of azo group transfer from trans to cis, the Ribavirin release rate out from hydrogel was accelerated. By comparison, the release rate of C1 → C4 was less than that of T1 → T4. For the series of C1 → C4, their lower release rate was attributed to their smaller porosity as compared with T1 → T4.

The extent of conformation of the azo group is greater in series of T1 → T4 than the series of C1 → C4. This was likely to be the result of the presence of cavities, which allowed more room for the isomerization of the azo group when irradiating. Such photoinduced conformational changes of the azo group were able to greatly affect their binding affinity for Ribavirin. These results indicated that there was steric hindrance of the networks to the passage of Ribavirin to the azo groups of cross-linked polymers.

4. Conclusion

APABS was successfully synthesized and was used to prepare two kinds of photoresponsive hydrogel with UV and visible light via photopolymerization technology. SEM and drug release results indicated that two series of photoresponse hydrogel exhibited obvious different photosensitive properties, which showed different internal structures and release mechanism. Such materials may not only lead to the fabrication of photoresponsive hydrogel but also provide a novel path to design smart medical materials.

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