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Preparation and Characterization of a Bioadhesive with Poly (vinyl alcohol) Crosslinking Agent

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ABSTRACT: Synthetic adhesives containing 3,4-dihydroxy-L-phenylalanine and its derivatives have strong adhesion strength and good biocompatibility, which make them prime candidates for adhesives or bioadhesives applications. In this study, a new photocurable poly (vinyl alcohol) (UV-PVA) derivative was prepared and used as crosslinking agent to further improve adhesion strength of dopamine methacrylamide (DMA) system. The structure of UV-PVA was confirmed, and the degree of acryloyl group substitution (DS) was easily varied from 10 to 40% by varying the molar ratio of acryloyl chloride to —OH of PVA. The effects of ultraviolet light intensity, content of DMA and DS values of PVA on the photopolymerization kinetics were studied, and the effects of DS value on the adhesive strength, swelling performance and cell attachment were also investigated. It was found that adhesive containing UV-PVA with 40% DS value yielded the highest adhesive strength, a relatively low swelling ratio and good biocompatibility. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: photocrosslinkable; adhesives; biomimetic; poly (vinyl alcohol); mechanical properties

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INTRODUCTION

Natural adhesives are common in many biological systems and are well known for their excellent strength and durability. So, they have been suggested for use as adhesives for biotechnological purposes, such as medical and dental materials.[1–4] Marine mussels are examples of organisms able to affix themselves to virtually any surface even in the presence of waves and tides.[2,5–7] Surprisingly, mussels can even stick to polytetrafluoroethylene (PTFE, Teflon).[5,7] Although the exact structure of such adhesives is not yet known, now it is widely recognized that a high content of the catecholic amino acid 3,4-dihydroxy-L-phenylalanine (DOPA) is central to curing of mussel adhesive proteins.[1,2,5,8] Generation of mussel glue is dependent on crosslinking of these DOPA proteins.[7] It is reported that both natural and synthetic adhesives containing DOPA and its derivatives have demonstrated strong interfacial adhesion strength. However, in general, it is complicated and expensive to extract a great quantity of proteins and polypeptides with DOPA.[5,8] Motivated by the belief that catechol incorporation into synthetic polymers will enhance their adhesive properties, a variety of functional synthetic materials have been developed, and many researchers have investigated catechol-containing linear or branched synthetic polymers as mimics of mussel protein.[9–11] Professor Bruce P. Lee's group has reported a lot of literatures about DOPA-modified poly (ethylene glycol) hydrogels, DOPA-modified acrylate derivatives, etc. The results showed that incorporating DOPA groups into the polymer structure significantly enhanced the dry-wet adhesive strength of materials.[12–14]

Poly (vinyl alcohol) (PVA), as a synthetic polymer, possesses many desirable properties, such as biodegradable, nontoxic, noncarcinogenic, good chemical and thermal stability and biocompatibility, which make it excellent biomaterial for pharmaceutical and biomedical applications, for instance, contact lenses, artificial heart valves, artificial blood vessels, drug delivery carriers, wound dressings, biodegradable scaffolds, cartilage, and artificial pancreas.[15–20] PVA has a simple chemical structure with abundant hydroxyl groups which have the potential to form hydrogen bond between molecules, or within different parts of a single molecule, also to be crosslinked by physical or chemical methods with multifunctional crosslinking agents as well as to be readily modified to attach growth factors, adhesion proteins, or other molecules of biological importance.[20–22] So, PVA has a great interest to be used in biomedical and pharmaceutical investigations. Schmedlen et al. prepared photoactive PVA hydrogels by grafting a photo-crosslinkable group on a fraction of the pendant hydroxyl chains, which could form

gelation within minutes at physiological pH and temperature in the presence of a nontoxic photoinitiator upon exposure to long wavelength ultraviolet (UV) light. And the mechanical properties of those materials could be tailored for a variety of soft tissue applications.[23]

Photopolymerization is a widely explored technology that has recently been recognized to have great potentialities in the bioadhesive field. Some of the most attributes are: rapid curing speed, possibility of carrying out photopolymerization *in vivo* or *ex vivo*, for fabrication of complex shaped polymeric matrices, spatial and temporal control of the polymerization process, versatility of formulation and application and ingredients can be stored in the most appropriate conditions until use.

In this study, we aim to develop a new kind of polymer crosslinking agent based on photocurable poly (vinyl alcohol) (UV-PVA) that reacts with dopamine methacrylamide (DMA) to improve its adhesive strength. The purpose of this study is to investigate the effect of the degree of acryloyl group substitution (DS) on the photopolymerization kinetics, adhesive strength, swelling performance and cell attachment.

MATERIALS AND METHODS

Materials

Dopamine-HCl was purchased from Brilliance Biochemical Co. (Beijing, China). PVA 1788 (88% hydrolyzed, average Mw 72600–81400 g/mol), methacrylate anhydride, DMEM and hoechst agent were purchased from Sigma-Aldrich Co. (Shanghai, China). Acryloyl chloride was purchased from Zhongsheng Huateng Technology Co. (Beijing, China). And α-hydroxy isobutyryl benzene (Darocur 1173) was obtained from Ciba-Geigy Chemical (Tom River, NJ). Mouse fibroblast (L929) was obtained from Department of Microbiology, Peking University Health Science Center (Beijing, China). N-methylpyrrolidone (NMP), triethylamine and other reagents were purchased from Beijing Chemical Agent Co (Beijing, China).

Synthesis of DMA

DMA was synthesized similar to the method established by Haeshin Lee et al.[8] Thirty-eight grams of $Na_2B_4O_7{\cdot}10H_2O$ and 8 g of $NaHCO_3$ were dissolved in 200 mL of deionized water and bubbled with N_2 for 0.5 h in a 500 mL three-necked round bottom flask equipped with stirrer at room temperature. Ten grams of dopamine-HCl was then added, followed by the dropwise addition of 9.8 g methacrylate anhydride in tetrahydrofuran within 3 h. The reaction mixture was stirred 12 h at room temperature with N_2 bubbling. The aqueous mixture was filtrated, and then the pH of the aqueous solution was reduced to less than 2 by hydrochloric acid and extracted with 200 mL ethyl acetate three times. Finally, the three ethyl acetate layers were collected, dried over anhydrous $MgSO_4$, and then the ethyl acetate was evaporated using a rotary evaporator at 35°C to reduce the volume to around 110 mL. Then, 700 mL of hexane was added with vigorous stirring and the suspension was held at room temperature overnight. The product was recrystallized from hexane and dried to yield 7.34 g of gray solid. ^{1}H NMR analysis was conducted to verify the formed product.

Preparation of UV-PVA

UV-PVA with acryloyl group was prepared by the esterification reaction of acryloyl chloride with PVA molecular as shown in Figure 1. 1.1 g PVA 1788 was dissolved in 110 mL NMP at 50°C for 1.5 h in a 250 mL four-necked round bottom flask equipped with stirrer, thermometer, dropping funnel and reflux condenser. Upon cooling to room temperature, 3.4 mL triethylamine (TEA) was then added, followed by the dropwise addition of 2 mL acryloyl chloride in NMP as slowly as possible. The reaction mixture was stirred for 1 h at 50°C. Then a large excess of 1mol/L HCl was added to the reaction mixture, and then dialyzed for 1 week. The product was obtained through freeze-dried process. The PVA derivatives with different DS value could be achieved by adjusting the molar ratio of acryloyl chloride to the hydroxyl group of PVA.

Preparation of DMA/UV-PVA Gel by Photopolymerization

DMA/UV-PVA gel was achieved by mixing 1.0 wt % photoinitiator Darocur 1173 (denoted as D-1173), 1.0 wt % UV-PVA as crosslinking agent and monomer DMA (30, 40, 50 wt %) in NMP solution. Then the solution was injected in a rubber mold (disks, 1.0 cm in diameter, 2.0 mm thick) between two glass slides. The mold was placed under UV light and the disk-shaped gels were obtained by UV irradiation at wavelength 365 nm for 15 min. Gels without PVA were also made for comparison purpose. Three samples were measured for each experiment.

CHARACTERIZATION METHODS

Fourier Transform Infrared Reflection

The Fourier transform infrared reflection (FTIR) spectra of pure PVA and UV-PVA with different DS values were recorded at room temperature by using a Nicolet 5700 instrument (Nicolet Instrument, Thermo Company, Boston, MA) over the wave number range of 4000–400 cm^{-1}.

^{1}H NMR Analysis

^{1}H NMR analysis was conducted to verify structure of DMA and UV-PVA by using a Bruker AV 600 MHz instrument (Bruker AV spectrometer at 600 MHz, Bruker, Germany) using deuterated DMSO solvent.

Photopolymerization Kinetics Study of DMA/UV-PVA System

Real time infrared reflection (RTIR) (Nicolet 5700 Instrument, Thermo Company, Boston, MA) was used to monitor photopolymerization kinetics of DMA/UV-PVA gels by quantifying the conversion of double bond. The double bond conversion was monitored by the absorbance change of the =C—H peak area ranging from 6101 to 6261 cm^{-1} in the near-IR range.[24] The effects of UV light intensity (10 mW/cm^2, 20 mW/cm^2, 30 mW/cm^2), content of DMA and different DS values of PVA on the photopolymerization kinetics were investigated.

Swelling Behavior of DMA/UV-PVA Gel

DMA/UV-PVA gels were immersed in sterile phosphate buffered saline (PBS, pH 7.4) at 37°C. Swollen gels taken out from the solution at regular intervals were dried superficially with filter paper and weighted till a constant weight was reached for each sample. Three samples were measured for each experiment. The degree of swelling (Q) is expressed as the mount of absorbed water per gram of gel during a regular time interval, which is calculated by an equation as follows:

$$Q(\%) = (W_2 - W_1)/W_1 \times 100\%$$

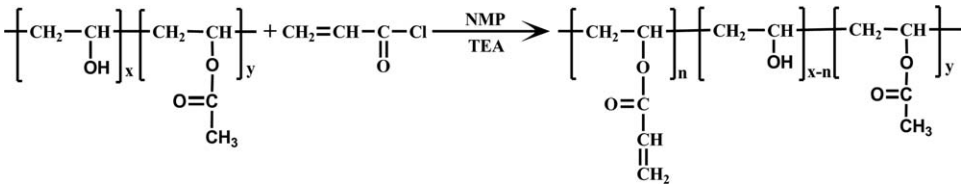

Figure 1. Schematic of the synthesis of UV-PVA.

where W_2 and W_1 are the weights of the same sample in the swollen and dry state, respectively.

Adhesion Strength Measurement

To evaluate the macro scale adhesion strength of adhesive gel, each DMA/UV-PVA solution was applied between two glasses (5 mm × 20 mm × 50 mm). Bonding area was 20 × 15 mm in which the DMA/UV-PVA solution was spread uniformly. The adhesive area was irradiated under UV light source (20 mW/cm^2) for 15 min to form gel. The gels were kept at 25°C for 24 h, and then the samples were tested by using a universal testing machine (Model 1185, Instron, Boston, MA) with a crosshead speed of 5 mm/min at room temperature. Five samples were measured for each experiment, and the average of these values was recorded.

Cell Attachment of DMA/UV-PVA Gel

The prepared gels were soaked in 250 mL phosphate buffer solution (PBS pH = 7.4) for 24 h before sterilization with highly compressed steam for 20 min, and then they were transferred to a 24-well plate. One millilitre of L929 suspension with 1.5 × 10^{4}cell/mL was seeded on the samples. After culturing for 48 h, collected samples were rinsed twice with PBS in order to remove nonadherent cells. And subsequently fixed by 75% alcohol solution, hoechst staining, the samples were observed by the fluorescence microscope (HZ— 9610K, Beijing, China) and scanning electron microscopy (SEM) (S-450, Tokyo, Japan).

RESULTS AND DISCUSSION

^{1}H NMR Analysis of DMA

As shown in Figure 2, two important signals were clearly observed in the ^{1}H NMR spectroscopy. Signals in the range of δ 6.62-6.33 ppm were corresponded to the hydrogen in the benzene ring (3H, $C_6\mathbf{H}_3(OH)_2$—) (labeled a, b, c), and signals at δ 5.61 and 5.29 ppm were indicative of the acryl group (2H, —C(=O)—C(—CH_3)=C$\mathbf{H}_2$) (labeled i, h). Other signals of DMA were as follows: 7.91 (1H, $C_6H_3(OH)_2$—CH_2—CH_2(N**H**)—) (labeled f), 3.23 (2H, $C_6H_3(OH)_2$—CH_2—C$\mathbf{H}_2$(NH)—C(=O)—) (label e), 2.55 (2H, $C_6H_3(OH)_2$—C$\mathbf{H}_2$—CH_2(NH)—C(=O)—) (labeled d), 1.83 (3H, —C(=O)—C(—C$\mathbf{H}_3$)=CH_2) (labeled g). Obviously, DMA was successfully synthesized.

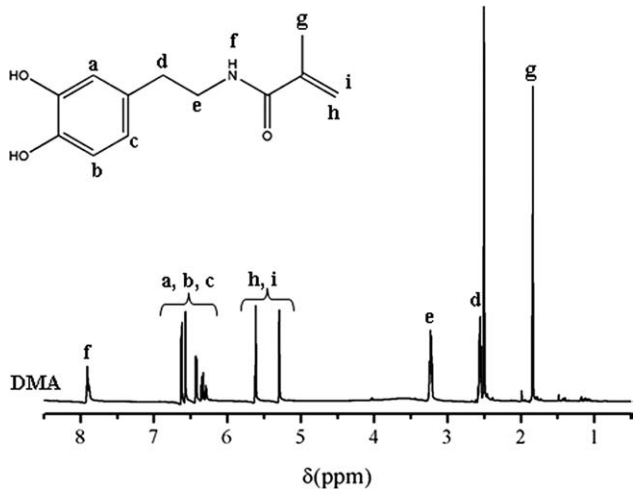

Figure 2. ^{1}H NMR spectra of DMA.

^{1}H NMR and FTIR Analysis of UV-PVA

The UV-PVA was prepared via esterification process of acryloyl chloride to —OH of PVA at 50°C. So it would be noted that self-polymerization of acryloyl chloride as side reaction would affect the reaction adversely. Three UV-PVA samples (denoted as UV-PVA1-3) with different DS values were as shown as Table I.

As shown in Figure 3, the structure of UV-PVA was verified by the ^{1}H NMR spectroscopy in deuterated DMSO, where signals in the range of δ 5.90–6.27 ppm (labeled a, b, c) corresponded to the acryl group. DS value was calculated from the integral ratio of signals at 6.12 ppm (CH_2=C**H**C(=O)—) and 3.80 ppm (—CH_2C**H**— from PVA).[15] As shown in Table I, with the molar ratio of reactant varied, DS value also changed. When the molar ratio of reactant increased to 1.0, the DS value reached to 40%, which was the highest DS value.

FTIR spectra of PVA and UV-PVA were provided in Figure 4. Figure 4(a) showed the principal spectral features in PVA: 3420 cm^{-1} (O—H stretch), 1720 cm^{-1} (C=O stretch) and 814 cm^{-1} (C=C stretch). After esterification reaction with acryloyl chloride, the FTIR spectrum for all UV-PVA samples showed relative absorbance intensities at 814 and 1720 cm^{-1}, which were indicative of the double bone of the acryloyl group and the carbonyl group respectively, were significantly increased. The broad band at around 3420 cm^{-1} was sharpened with the introduction of carbonyl group. It was obvious that increasing the DS value caused an increase in the relative absorbance intensities. When the DS value reached to 40%, the relative absorbance intensities at 814 and 1720 cm^{-1} of UV-PVA2 was the highest.

Table I. Molar Ratio of Reactant and DS Value of UV-PVA

Sample name	The molar ratio of acryloyl chloride to -OH	DS[a] value (%)
UV-PVA1	0.5	10
UV-PVA2	1.0	40
UV-PVA3	1.5	15

[a]DS value was calculated from ^{1}H NMR spectroscopy.

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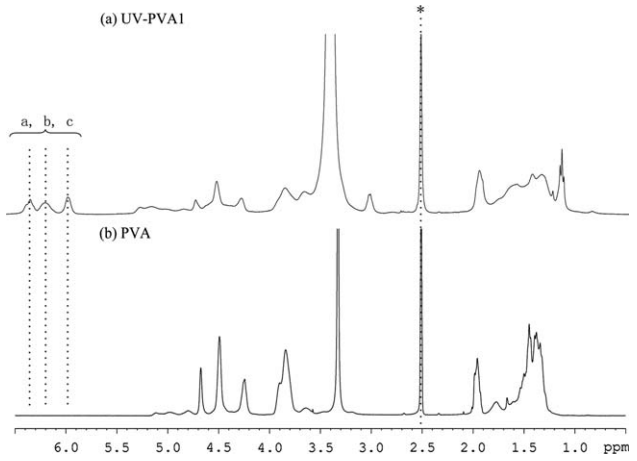

Figure 3. ^{1}H NMR spectra of PVA and UV-PVA.

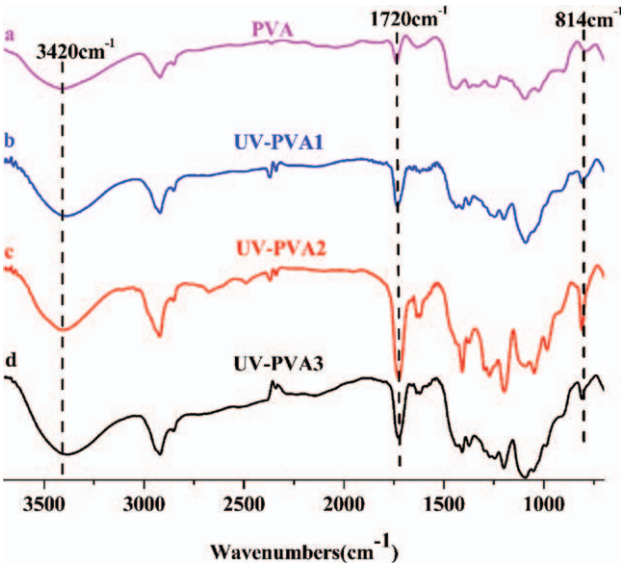

Figure 4. FTIR spectra of PVA and UV-PVA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Photopolymerization Kinetics Study of DMA/UV-PVA Gel

DMA/UV-PVA gel was prepared by mixing 1.0 wt % photoinitiator D-1173 and 30, 40, and 50 wt % DMA in NMP solution under UV irradiation, respectively. Gels only with DMA, containing neither pure PVA nor UV-PVA (denoted as Gel-x-0) and gels with pure PVA (denoted as Gel-x-4) were also made for comparison purpose. The composition of gels was listed in Table II, and RTIR was used to monitor photopolymerization kinetics of DMA/UV-PVA gels.

In Figure 5(a, b), the influence of UV light intensity on the photopolymerization kinetics of DMA/UV-PVA gels was shown. The polymerization rate and final conversion of the double bonds increased with increasing the UV light intensity from 10 to 20 mW/cm^2. And then increased the UV light intensity further, there no significant change was observed. This was because the higher UV light intensity could yield more radicals, and simultaneously, the more radicals could overcome oxygen inhibition more efficiently, which resulted in the shortening of the induction period.[25] However, a high UV light intensity would bring some damage to cell, a proper light intensity of 20 mW/cm^2 for the preparation of bioadhesive gel was chosen to ensure a rapid polymerization and low cytotoxicity. Figure 5(c) illustrated the effect of content of DMA on the photopolymerization kinetics. It was obvious that the more DMA, the faster polymerization rate and the higher final conversion, which was because the more DMA yielded more double bonds. And Figure 5(d) showed the conversion of double bond vs. irradiation time of DMA/UV-PVA gels with different DS values of UV-PVA.

Table II. The Composition of Gels

Sample code		UV-PVA (wt %)			Pure PVA (wt %)	DMA (wt %)	NMP (wt %)	D-1173 (wt %)
		UV-PVA1	UV-PVA2	UV-PVA3				
Gel-1	Gel-1-0					30	69	1
	Gel-1-1	1				30	68	1
	Gel-1-2		1			30	68	1
	Gel-1-3			1		30	68	1
	Gel-1-4				1	30	68	1
Gel-2	Gel-2-0					40	59	1
	Gel-2-1	1				40	58	1
	Gel-2-2		1			40	58	1
	Gel-2-3			1		40	58	1
	Gel-2-4				1	40	58	1
Gel-3	Gel-3-0					50	49	1
	Gel-3-1	1				50	48	1
	Gel-3-2		1			50	48	1
	Gel-3-3			1		50	48	1
	Gel-3-4				1	50	48	1

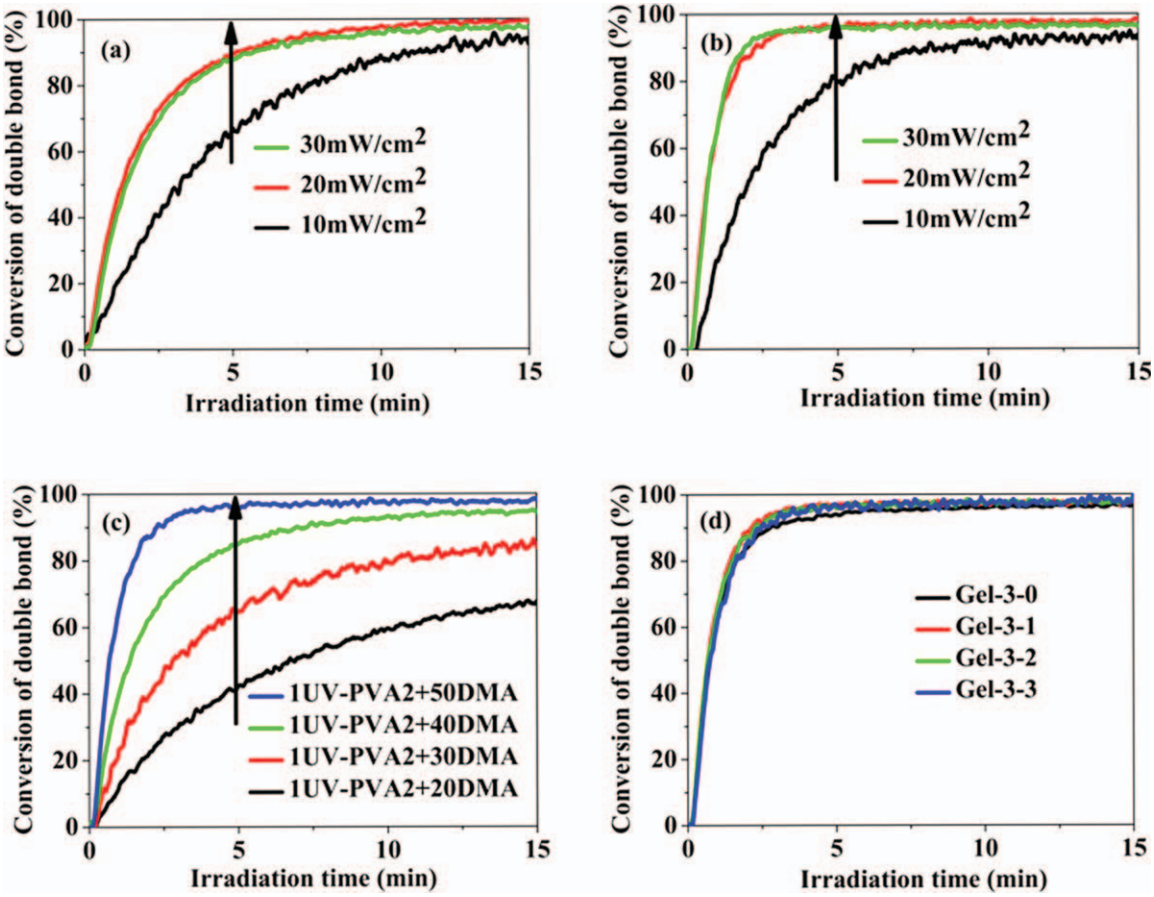

Figure 5. Conversion of double bond as a function of irradiation time. (a) different UV light intensity (40DMA + 1UV-PVA2) (b) different UV light intensity (50DMA + 1UV-PVA2) (c) different DMA content (UV-PVA2 used as crosslinking agent) (d) different DS value of UV-PVA initiated by 20mW/cm^2 in the presence of 1.0 wt % D-1173. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Compared to gels without UV-PVA crosslinking agent, introduction of UV-PVA with different DS value had no significant influence on photopolymerization kinetics of gels. This was because the content of the double bonds of the crosslinking agent in the entire solution was relatively low.

Swelling Behavior of DMA/UV-PVA Gel

Figure 6 demonstrated typical swelling behavior of DMA/UV-PVA gel containing 50 wt % DMA as a functional of time. It could be seen that all gels had similar swelling behavior and reached swelling equilibrium around 44 h. As shown in Figure 6, although content of UV-PVA was only 1.0 wt %, it had slight effect on swelling kinetics of DMA/UV-PVA gels. As the DS value of UV-PVA decreased, swelling ratio increased, which was mainly due to the formation of more loosely crosslinked network.[26] With decreasing DS value, crosslinking density of DMA/UV-PVA gel decreased and molecular entanglement between DMA and UV-PVA was weakened, which resulted in improvement of its swelling ability. When the DS value of UV-PVA was 10%, Gel-3-1 reached the highest swelling equilibrium ratio about 27%.

Evaluation of Adhesion Strength

Lap-shear test was used to quantify the macro scale adhesion strength of DMA/UV-PVA gel. Figure 7 illustrated the effect of composition of gels on the tensile strength. The samples for lap-shear test were prepared as Figure 7(d) and executed as Figure 7(e).

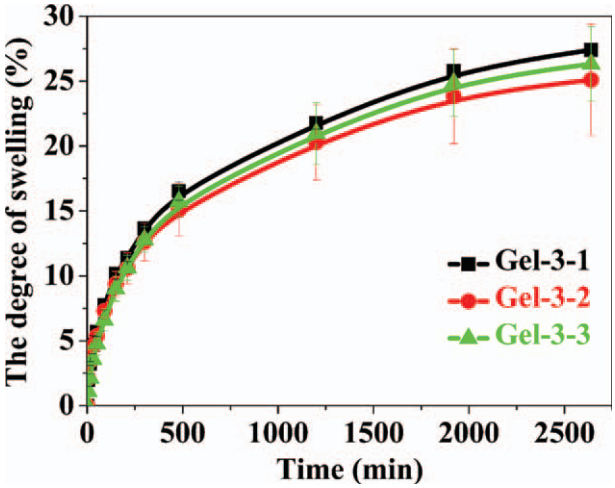

Figure 6. Swelling kinetics of DMA/UV-PVA gels containing 50 wt % DMA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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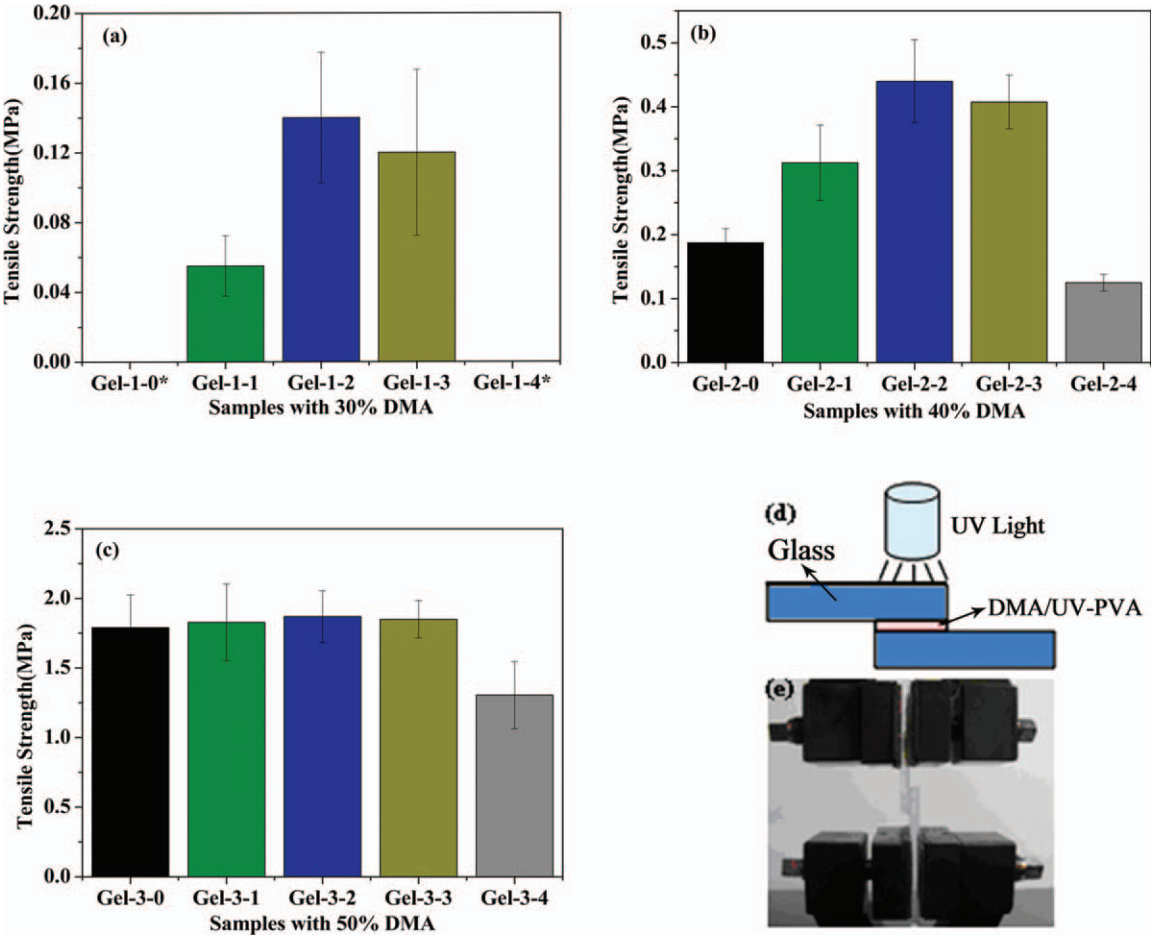

Figure 7. Adhesion strength test of DMA/UV-PVA gel. (a) 30DMA + 1UV-PVA (* Tensile strength of Gel-1-0 and Gel-1-4 couldn't test.) (b) 40DMA + 1UV-PVA (c) 50DMA + 1UV-PVA (d) preparation of lap-shear sample (e) schematic of tensile test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

As everyone knows, pure PVA can be used as adhesives. As a result, gels containing pure PVA were prepared for comparison purpose. As Figure 7(b, c) shown, it was surprising that gels only with DMA (denoted as Gel-x-0) were more effective in the tensile strength than gels containing pure PVA (denoted as Gel-x-4). It was because that the addition of pure PVA had a significant impact on solution viscosity which would affect the subsequent photopolymerization reaction adversely.

As shown in Figure 7(a, b), compared to gels only with DMA (denoted as Gel-x-0) and gels containing pure PVA (denoted as Gel-x-4), adhesion strength of DMA/UV-PVA gels (denoted as Gel-x-1, -x-2, and –x-3) were significantly higher. Especially, took gels containing 30 wt %DMA as examples, adhesion strength of Gel-1-0 and Gel-1-4 was too small, so it could not test by lap-shear test. However, from Figure 7(c), it seemed that the effect of containing UV-PVA was relatively limited, which was because that gels with high monomer content would form a more densely crosslinked network. In such case, the role of UV-PVA as crosslinking agent was not too obvious.

Theoretically, DMA containing DOPA was the key component in the gels. The more content DMA was contained, the higher adhesion was obtained. Moreover, the research results indeed confirmed this speculation, DS value had great influence upon adhesion strength of DMA/UV-PVA gel. The adhesion strength increased with increasing of DS value of UV-PVA. When the DS values increased to 40%, the adhesion strength reached the highest, and adhesion strength of gels with 30, 40, and 50 wt % DMA reached to 0.14MPa, 0.44MPa, and 1.87MPa, respectively.

Cell attachment of DMA/UV-PVA Gel

In this study, cell attachment measurement was conducted to evaluate the biocompatibility of DMA/UV-PVA gels. Considering that samples with smooth surface were required, the results of Gel-3-1 and Gel-3-3 were shown. Surface of Gel-3-2 sample was not smooth enough, which was due to a faster polymerization rate and a higher final conversion caused by a more content of double bonds.

After culturing for 48 h, collected samples were rinsed twice with PBS, subsequently fixed by 75% alcohol solution, hoechst staining, the samples were observed by the fluorescence microscope and SEM. As Figure 8(a) shown, plenty of L929 cells were cultured on the surfaces of Gel-3-1 and Gel-3-3, and cell nucleuses were round. In addition, as Figure 8(b) shown, through

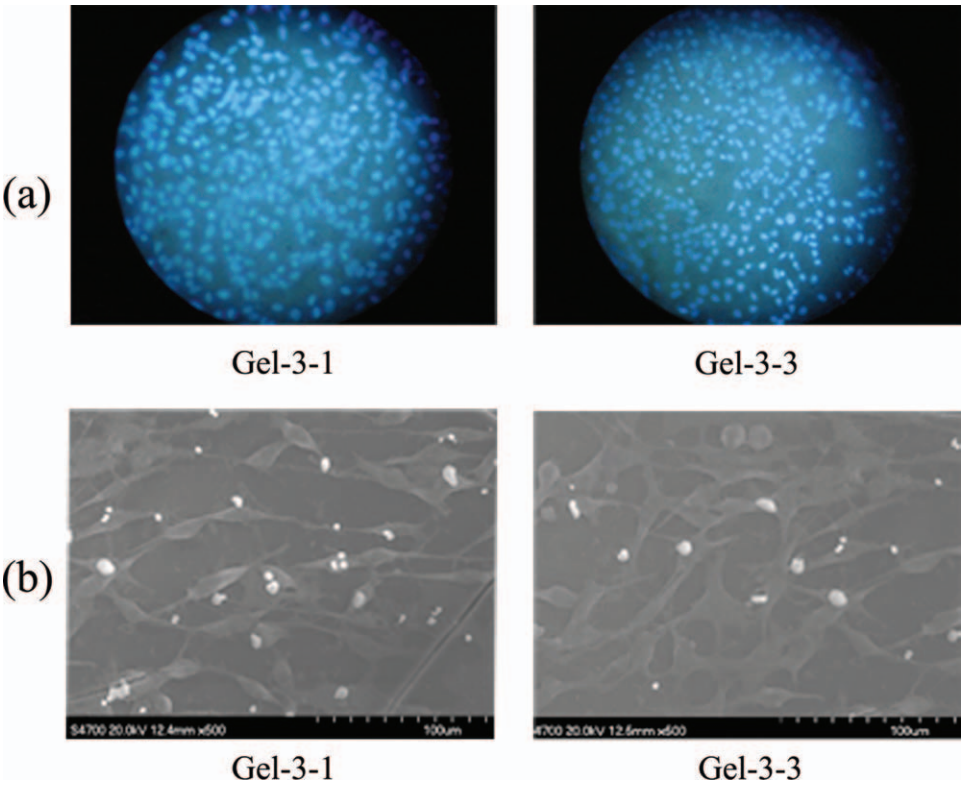

Figure 8. Images of L929 cell seeded on DMA/UV-PVA gels. (a) fluorescence microscope images (×200 magnification) (b) scanning electron microscopy images (×500 magnification). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the SEM observation, it could be found that L929 cells were not only attached but also had assumed the long, spindle morphology characteristic, which was typical of live fibroblastic cells and normal cell nucleus morphology. The all results suggested that good cell viability on the DMA/UV-PVA gels.

CONCLUSIONS

In this study, a new photocurable bioadhesive system with DOPA functional group and PVA crosslinking agent was studied. Monomer DMA and UV-PVA derivatives containing photosensitive groups were prepared and characterized by FTIR, ^{1}H NMR spectroscopy. And the degree of acryloyl group substitution (DS) of UV-PVA was easily varied by varying the molar ratio of acryloyl chloride to —OH of PVA. Physical/mechanical properties of the adhesive gels including swelling ratio, adhesion strength were evaluated. It was found that adhesive containing UV-PVA with 40% acryloyl group as crosslinking agent yielded the highest adhesive strength and a relatively low swelling ratio. Cell attachment measurements showed that good cell viability of L929 cell on the adhesive gels. The results indicated that this gel could be a good candidate for bioadhesives.

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