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Trifunctional cross-linker trimethylol melamine enhancing adhesive force of PVA hydrogels

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ABSTRACT: Adhesive force is a critical feature *in vitro* for soft hydrogels as wound dressing. Here we employ trimethylol melamine as a tri-functional cross-linker to enhance the adhesive force of poly(vinyl alcohol) (PVA) hydrogels. First, trimethylol melamine was prepared using melamine and formaldehyde by a condensation reaction. Then PVA was cross-linked in an aqueous medium to form hydrogels by using trimethylol melamine as a cross-linker. It was found that trimethylol melamine cross-linked PVA hydrogels (TMCPVA) exhibited a good adhesion property with a low degree of cross-linking and no residue after the TMCPVA peeled from skins, indicating the TMCPVA were suitable for adhesive wound dressing. Moreover, their structures, morphology and adhesive forces were characterized by Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and texture analyzer (TA). The results indicated that TMCPVA would be promising wound dressing materials with biocompatible and well-adhesive properties. © 2016 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43774.

KEYWORDS: adhesives; biocompatibility; biomaterials; gels; hydrophilic polymers

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INTRODUCTION

Hydrogels were defined as three-dimensional polymer network consisting of a large amount of water as a solvent.[1,2] Polyvinyl alcohol (PVA) has been considered as a suitable biomaterial for fabricating biomedical hydrogels owing to its good characteristics, such as biocompatibility,[3] highly hydrophilic,[4] excellent mechanical strength, thermal stability, absence of toxicity,[5] and relative low cost. As a result, PVA hydrogels were widely used in the field of tissue engineering, such as vascular cell culture, vascular implanting,[6] heart valves,[7] cartilage substitute, contact lenses, and corneal implants.[8] Especially, hydrogels could absorb leaking body fluids and facilitate the creation of a moist environment as wound dressings. The moist environment would encourage rapid granulation tissue formation and accelerate wound healing.[9]

TMCPVA could be divided into physical and chemical hydrogels.[10] Generally, TMCPVA were obtained by a cross-linking process of polymers, which might be achieved through a chemical reaction using high energy irradiation[11–13] or through a physical reaction of polymer crystallization[14,15] and/or hydrogen bonds. For chemically cross-linking PVA hydrogels, glutaraldehyde as a traditional bifunctional cross-linker[16] could joint two PVA molecular chains so that the polymer network structure wasn't enough stable.

For physical PVA hydrogels, the application was limited by the poor mechanical properties due to the weak interaction. To fabricate TMCPVA with stable network, it is essential to design and synthesize a multifunctional cross-linker. Moreover, enhancing the interface adhesion forces between materials and skins is also important to be considered for the design of wound dressing.[17] It was found that the application of biomaterials in tissue engineering and cell adhesion has been reported *in vivo*. However, PVA hydrogels were seldom used *in vitro* medical devices, such as wound dressing, eye patch and health care applicator, due to the adhesion loss of highly cross-linked PVA hydrogels.

Our strategy was to achieve TMCPVA with a good adhesive property and biocompatibility. The TMCPVA were prepared by the introduction of a novel tri-functional cross-linker to control the adhesion force. In addition, we designed and synthesized the structure of PVA hydrogels' network by trimethylol melamine. Because of its multifunctional structure, the consumption of cross-linking agent could be reduced. Meanwhile the adhesive properties of TMCPVA could be retained. The hydrogels are promising for not only biomedical applications but also daily necessities such as environmental friendly glue, pipe joints, and so on.

EXPERIMENTAL

Materials

PVA 1799 (alcoholysis degree 98–99%) and melamine (99%) were supplied by Aldrich Chemical Company US. Formaldehyde

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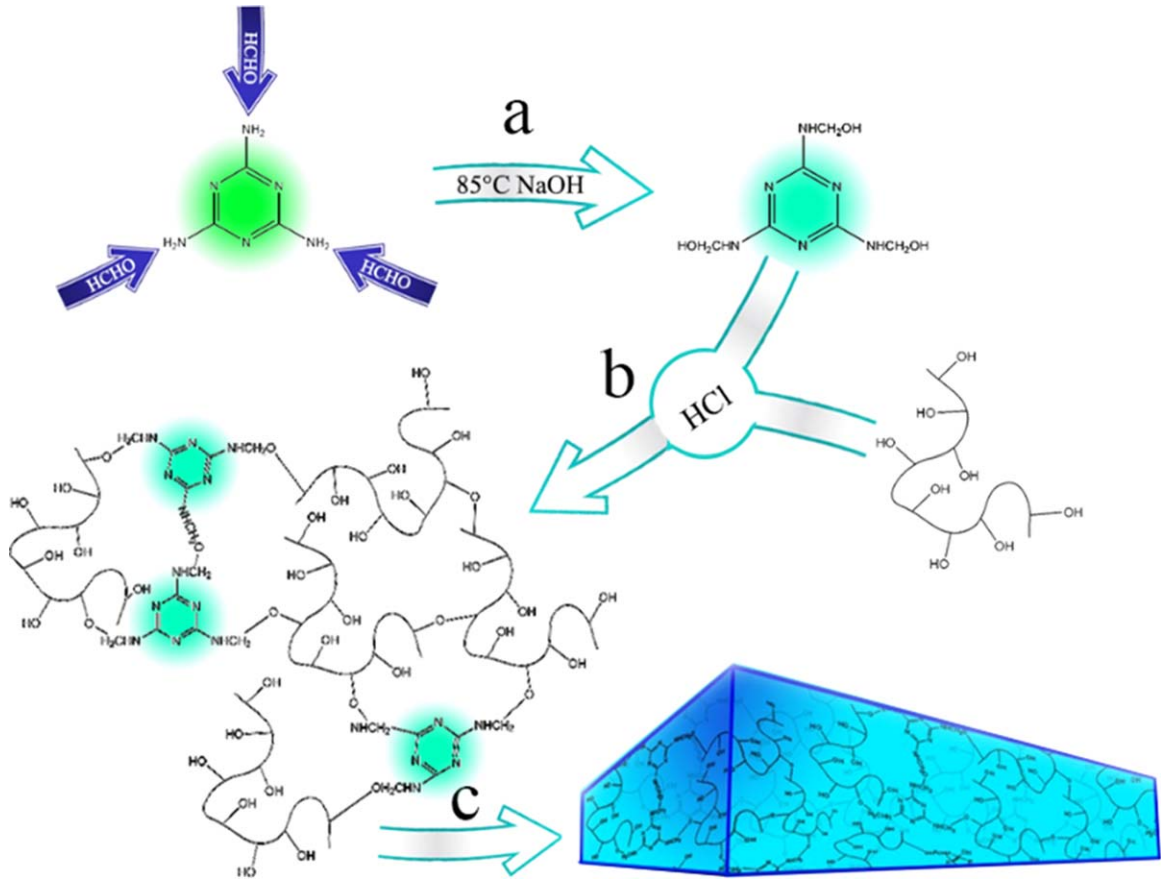

Figure 1. Schematic illustration of PVA hydrogels: (a) synthesis of cross-linkers, (b) PVA chains cross-linking, (c) PVA hydrogels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(37.0 wt % AP) was supplied by Fine Chemical Tianjin Yong Sheng, China. Sodium hydroxide (NaOH, AP) and hydrochloric acid (HCl, 36.46 wt %, AP) were supplied by Beijing Chemical Works, China. Deionized water was made by Water Purification System Certificate of Conformity.

Cross-linker Synthesis

The pH of formaldehyde solution was adjusted to 8.5 by gradually adding NaOH (0.1 M) at 25 °C. Melamine [n(Formaldehyde): n(Melamine) = 3:1] was dissolved in formaldehyde solution at 85 °C for 20 min to synthesize the cross-linker [shown in Figure 1(a)].

Preparation of TMCPVA

Different contents of PVA were dissolved in an aqueous solution at 95 °C for 30 min. These PVA solutions were cooled to room temperature prior to use. Then the pH of the solution was adjusted to 4.8 by gradually adding HCl (0.1 M) solution. The cross-linker was added into PVA aqueous solutions at 50 °C for 2 h to synthesize the TMCPVA. It was shown in Figure 1(b,c). We had synthesized TMCPVA with different components shown in Table I. The chemical compositions of materials were represented by the sample name: $xMP_{n\text{-}m}$.[x stands for PVA wt %, n-m means m(Crosslinker):m(PVA)] The detailed preparation process of TMCPVA was shown in Figure 2.

These PVA solutions were added to the little bottles and carried out at different conditions for 12 h, including drying by an oven (60 °C), storing at room temperature (25 °C), and keeping in a refrigerator (−20 °C).

PVA Hydrogels Preparation by Freezing–Thawing and Radiation Methods

Crystallization. PVA hydrogels were also obtained by freezing–thawing cycles.[18,19] A 1.915 g of PVA was added to 30 mL deionized water, which was stirred continuously at 95 °C for 30 min to form a homogeneous solution. The PVA aqueous was then poured into petri dishes, followed by freezing at −20 °C for 24 h and thawing at 25 °C for 6 h. The cycle number was three times.

Electron Beam Radiation. A 1.915 g of PVA was added to 30 mL deionized water, which was stirred continuously at 95 °C for 30 min to form a homogeneous solution. Irradiation was conducted using a 6 MeV electron accelerator (ELU-6, Eksma, Russia), yielding an average dose rate of 32 kGy min^{-1}. PVA hydrogels were formed after 20 min.

Chemical Cross-linking Intensity

TMCPVA were put into water at 99 °C to study its cross-linking degree. The physical interaction was gradually destroyed with time increasing, while the component of chemically cross-linked PVA hydrogels precipitated to the bottom about 6 h. Finally, the amount of hydrogels kept constant. The residue could be considered as chemical cross-linking hydrogels.

Table I. The Components of the Samples in PVA Hydrogels

Sample	m(HCHO)/g	m(Mel)*/g	m(PVA)/g	**W(PVA)**	**C:P***	Hydrogel time	Residue
3MP1-10	0.0386	0.0541	0.9278	**3%**	**1:10**	*No*	-
3MP2-10	0.0772	0.1082	0.9278	**3%**	**2:10**	*No*	-
3MP3-10	0.1158	0.1623	0.9278	**3%**	**3:10**	*72h*	*Have*
4MP1-10	0.0521	0.0729	1.2500	**4%**	**1:10**	*No*	-
4MP2-10	0.1042	0.1458	1.2500	**4%**	**2:10**	*No*	-
4MP3-10	0.1563	0.2187	1.2500	**4%**	**3:10**	*24h*	*Have*
5MP1-10	0.0657	0.0921	1.5789	**5%**	**1:10**	*No*	-
5MP2-10	0.1314	0.1842	1.5789	**5%**	**2:10**	*12h*	*Have*
5MP3-10	0.1971	0.2763	1.5789	**5%**	**3:10**	*12h*	*Not*
6MP1-10	0.0832	0.1117	1.9149	**6%**	**1:10**	*No*	-
6MP2-10	0.1664	0.2234	1.9149	**6%**	**2:10**	*12h*	*Not*
6MP3-10	0.2496	0.3351	1.9149	**6%**	**3:10**	*6h*	*Not*
7MP1-10	0.0941	0.1317	2.2581	**7%**	**1:10**	*24h*	*Have*
7MP2-10	0.1882	0.2634	2.2581	**7%**	**2:10**	*6h*	*Not*
7MP3-10	0.2823	0.3951	2.2581	**7%**	**3:10**	*3h*	*Not*
8MP1-10	0.1087	0.1522	2.6087	**8%**	**1:10**	*12h*	*Not*
8MP2-10	0.2174	0.3044	2.6087	**8%**	**2:10**	*3h*	*Not*
8MP3-10	0.3261	0.4566	2.6087	**8%**	**3:10**	*1h*	*Not*
9MP1-10	0.1236	0.1731	2.9670	**9%**	**1:10**	*3h*	*Not*
9MP2-10	0.2472	0.3462	2.9670	**9%**	**2:10**	*1h*	*Not*
9MP3-10	0.3708	0.5193	2.9670	**9%**	**3:10**	*1h*	*Not*
10MP1-10	0.1389	0.1944	3.3333	**10%**	**1:10**	*1h*	*Not*
10MP2-10	0.2778	0.3888	3.3333	**10%**	**2:10**	*1h*	*Not*
10MP3-10	0.4167	0.5832	3.3333	**10%**	**3:10**	*1h*	*Not*

Mel means Melamine; C:P means m(Cross-linker):m(PVA).

Figure 2. Schematic diagram of PVA hydrogels preparation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

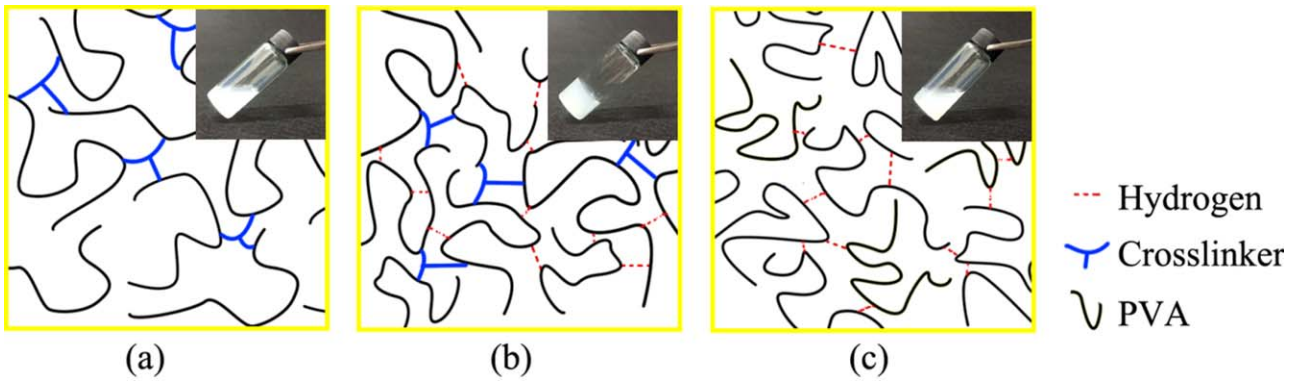

Figure 3. Schematic illustration of PVA hydrogel structure at different temperatures: (a) 60 °C, (b) 25 °C, (c) −20 °C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FTIR Analyses

The hydrogel samples were freeze-dried and pulverized. IR spectra of samples using KBr as pellets were recorded by FTIR (AVATAR-360; Nicolet).

Swelling Measurements

The hydrogel samples had been prepared to investigate the properties of swelling equilibrium in water. To reach the swelling equilibrium, the samples were soaked in distilled water for over 4 days at room temperature. The equilibrium swelling ratio was experimentally determined, and the percentage of swelling was calculated by eq. (1).

$$\text{Swelling} = \frac{W_s - W_i}{W_i} \times 100\% \quad (1)$$

where W_s is the weight of the swollen hydrogel at 25 °C and W_i is the weight of the hydrogel at an initial state without drying.

SEM Observation

The morphological structures of PVA hydrogels were observed by JSM-6510 scanning electron microscope of JEOL, Japan. Prior to examination, the samples were freeze-dried and the sections of samples were coated with platinum.

Adhesive Forces Measurements

A Texture Analyzer CT3 4500 instrument was used to measure adhesive forces of TMCPVA (10 mm width, 100 mm length) against the rigid steel sheet surface at room temperature (25 °C) with a 5 N load. The adhesion test was carried out at a rate of 0.5 mm s^{-1} and a peel angle of 90°. The steel sheet was cleaned with acetone to remove impurities on its surface before the experiment.

RESULTS AND DISCUSSION

Formation of TMCPVA

The sample 5MP3-10 took about 12 h to form hydrogel at 25 °C, however, the other samples at 60 °C and −20 °C still kept solution status. The above phenomenon could be explained by the different bonding status at different temperature which was illustrated in Figure 3. When the PVA solution was put at 60 °C, the PVA chains could be chemically cross-linked by trimethylol melamine. However, hydrogen bonds in hydrogels couldn't be formed at 60 °C.[20] The stretch capability of PVA chains at 60 °C were better than that at 25 °C or −20 °C, so that there were too few chains entanglements in the solution [Figure 3(a)]. (The chains curly degree has a negative correlation with temperature, so that there were too few chains entanglements in the solution at 60 °C [Figure 3(a)]. When the solution was put at 25 °C, the covalent bonds and hydrogen bonds in TMCPVA could be formed, so that the solution was easier to transform into hydrogels [Figure 3(b)]. When the solution was set at −20 °C, the formation of polymer network was only attributed to hydrogen bonds and chain entanglements because there was not sufficient energy to form covalent bonds in hydrogels [Figure 3(c)].

The formation time of TMCPVA was different for TMCPVA with different contents of PVA and cross-linker, which was shown in Table I. With increasing PVA contents, more PVA chains would be existed in solutions and the formation time was shortened. Moreover, the cross-link density would increase with the increase of the cross-linker content, leading to the formation of hydrogels network and reducing the hydrogels formation time.

Physical cross-linking hydrogels were formed by physical interactions (such as hydrogen bonds, Van der Waals forces, and so on), which was gradually destroyed at 99 °C in aqueous solutions with the time increasing.[20] As a result, we placed the sample 5MP3-10 into deionized water at 99 °C and observed the possible experimental phenomena. One hour later, the volume of hydrogels become larger than the original state, which could be explained by the swelling rate of the hydrogel was greater than the degradation rate. Moreover, a lot of bubbles appeared in hydrogels. Six hours later, the hydrogel was broken into fragments because the main structure of the hydrogel was broken into pieces due to the gradual destroying of hydrogen bonds. The photos of the hydrogel in different conditions were difficult to be recognized, so we took schematic diagram (Figure 4) for showing the state of hydrogels. The remaining amount of hydrogel fragments was no longer reducing for a long time, which was a favorable evidence for chemical cross-linking presented in the hydrogel because the energy couldn't destroy the covalent bonds. Therefore there is a slight cross-linking degree in the structure of TMCPVA.

FTIR Analyses. The structure of TMCPVA was confirmed by FTIR.[21] In the FTIR spectrum of PVA hydrogel (Figure 5), the

Figure 4. The PVA hydrogel changed from block to fragment at 99 °C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

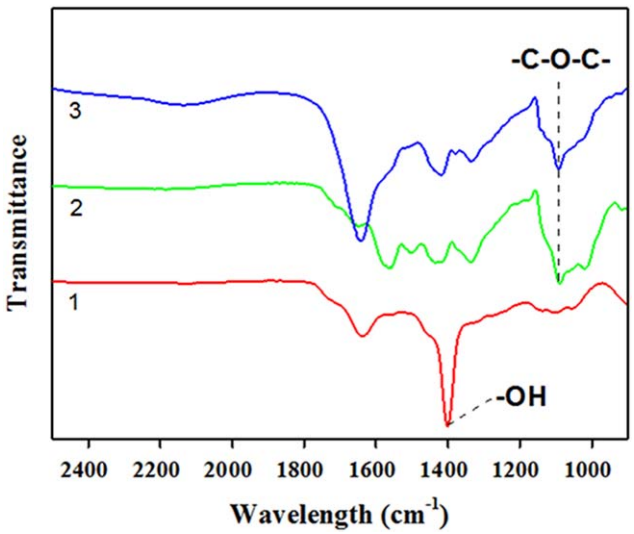

Figure 5. FTIR spectra of (1) PVA, (2) 9MP1-10, (3) 6MP2-10. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

1088 cm^{-1} band was associated with the stretching vibration of the ether bond C—O—C, which indicated the successful etherification between the —OH of trimethylol melamine and the —OH of PVA. The sharp absorption peak at 1398 cm^{-1} was assigned to —OH group in-plane bending vibration of PVA. The intensity of the peak at 1398 cm^{-1} in hydrogels was weaker than that of PVA. It indicated the cross-linking reaction between trimethylol melamine and PVA. Therefore, the FTIR demonstrated the chemical cross-linking structure existed in trimethylol melamine cross-linked PVA hydrogel which were prepared by us.

Swelling Measurements

The hydrogel samples were allowed to hydrate in distilled water at 25 °C. The water sorption uptake bars for 4MP3-10, 5MP3-10, 6MP3-10 and 6MP1-10, 6MP2-10, 6MP3-10 are illustrated in Figure 6. With the increase of PVA, the water uptake of PVA hydrogels decreased [Figure 6(a)]. The reason could be that the increasing content of PVA promoted the reduction in the average distance among cross-linking sites, which caused the increment in the actual cross-linking density and, in turn, lower water uptake of hydrogel samples.[22] The water uptake of 6MP2-10 was higher than that of 6MP3-10 due to higher concentration of trimethylol melamine. This explained that the increasing content of trimethylol melamine promoted the increment in the degree of cross-linking, which led to the substantial reduction in the PVA chain flexibility. However, there were not enough cross-linking points for 6MP1-10 and the swelling ratio couldn't be measured. Comparing Figure 6(a) and Figure 6(b), we found that the cross-linking agents would play a significant role in the swelling ratio.

Morphology and Adhesive Forces. According to the data, the content of PVA had a noticeable influence on the adhesive forces of the hydrogels which was shown in Figure 7(a). The load force of hydrogels increased with the increase of the PVA content. Adhesive forces were associated with the polarity[23–25] of hydrogels. Interestingly, the average thickness of the 6MP2-10, 8MP2-10, and 10MP2-10 network increased with the increase of the PVA content [Figure 7(b)]. Because of the increasing content of PVA, the average distance between PVA chains gradually reduced and the contact probability of PVA chains increased. Therefore, the hydrogen bonds were easily formed with the increase of PVA content which was illustrated in Figure 7(c), leading to the decrease of the surface polarity of

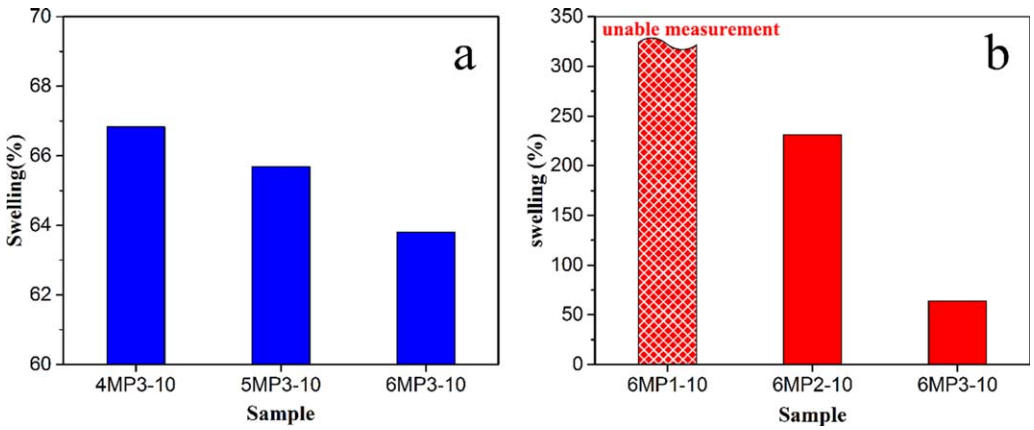

Figure 6. Swelling kinetics of PVA hydrogels in distilled water at 25 °C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

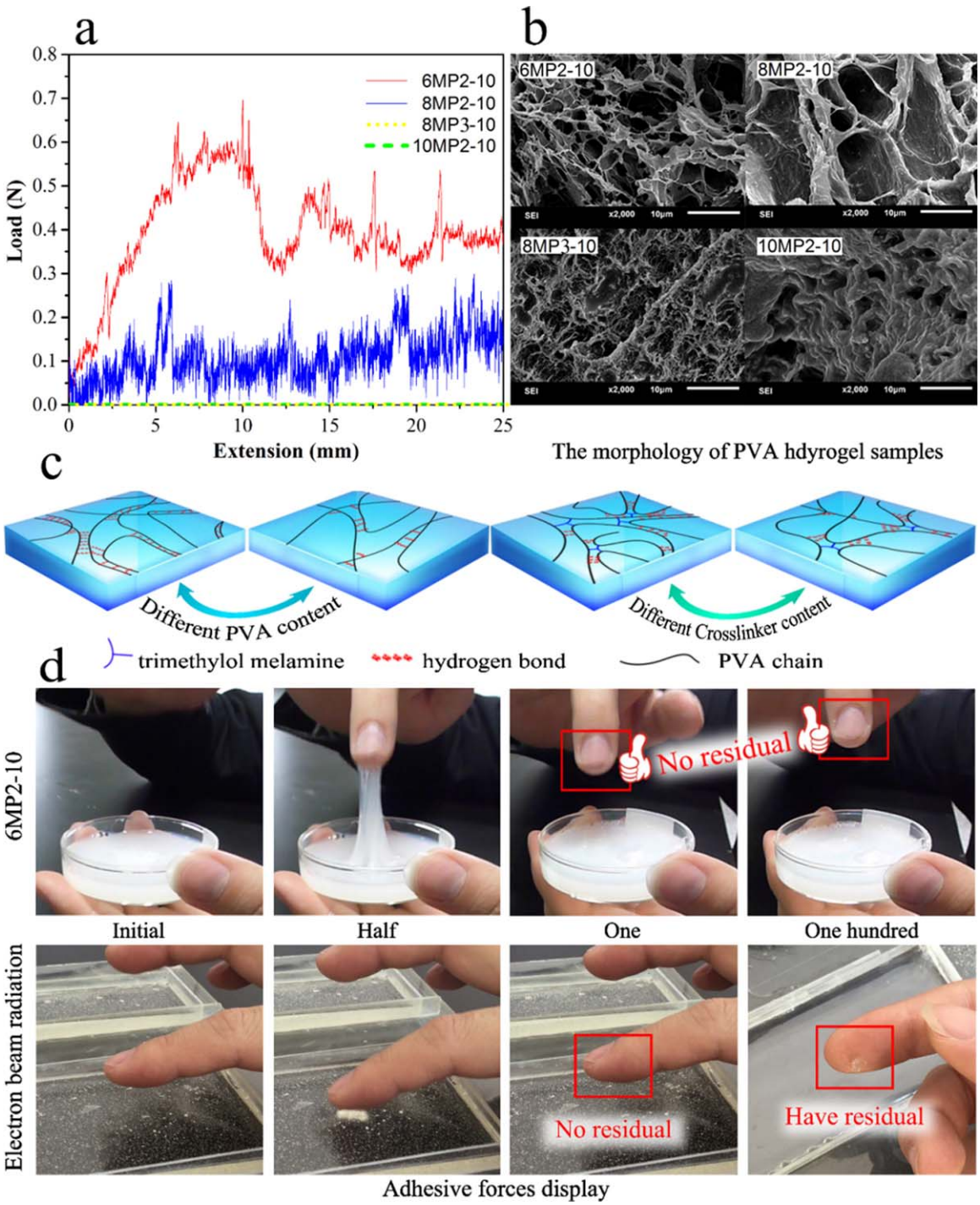

Figure 7. Morphology and adhesive forces of PVA hydrogel samples. (a) curve of adhesive forces data; (b) SEM photos; (c) the illustration of different PVA content and cross-linker; (d) adhesive forces display. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hydrogels. It was a favorable evidence for the reducing of adhesive forces with the PVA content increasing [Figure 7(a)].

Moreover, the cross-linker content had an effect on adhesive forces. Trimethylol melamine had a contribution to the formation of the network and the distance between PVA chains was reduced by cross-linking. It was found that the wall thickness of 8MP2-10 network was wider than 8MP3-10 and the structure of 8MP3-10 was much denser than that of 8MP2-10 for the same PVA content [Figure 7(b)]. As a result, the network of sample 8MP3-10 was more stable than 8MP2-10 with the increase of trimethylol melamine content when trimethylol melamine was uniformly dispersed in PVA hydrogels. The hydrogen bonds were easily formed to build the network of hydrogels [Figure 7(c)]. This results in the decrease of the —OH amount

and polarity in hydrogels, consequently, the adhesive forces of sample 8MP2-10 was higher than 8MP3-10.

Finally, the different preparation methods of hydrogels had an important impact on adhesive forces as well. It was found that the hydrogels, which were prepared by freezing and melting methods, didn't have any adhesive forces after three cycles. Crystallization had a negative correlation with the polarity of hydrogel surface, so the physical cross-linking PVA hydrogels didn't have any adhesive forces. Moreover, the hydrogels prepared by an electron beam radiation method had a little adhesive force which was shown in Figure 6(d). However, the adhesive force of chemically cross-linked hydrogels 6MP2-10 was higher than that of radiation cross-linking hydrogels. Besides, there was no residual gel on fingers when hydrogel was cross-linked by trimethylol melamine.

CONCLUSIONS

In this article, we prepared a highly adhesive and no residual hydrogel which was cross-linked by trimethylol melamine. The cross-linker trimethylol melamine could enhance the stability of PVA hydrogel network so that there were no residual gels after peel tests. Trimethylol melamine could provide three functional groups on one molecule, so that three pieces of PVA chains could be joint by one molecule. Because of its multifunctional groups, the consumption of cross-linking agent could be reduced. Meanwhile there was an increase of the surface polarity of hydrogels, so that the PVA hydrogel had high adhesive forces. According to its excellent adhesive properties, the application scope of hydrogels could be broadened in biomedical instruments, such as medical glue, wound dressing and health applicator.

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