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Research paper

# Bioadhesive film formed from a novel organic–inorganic hybrid gel for transdermal drug delivery system

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ABSTRACT

A novel organic–inorganic hybrid film-forming agent for TDDS was developed by a modified poly(vinyl alcohol) (PVA) gel using γ-(glycidyloxypropyl)trimethoxysilane (GPTMS) as an inorganic-modifying agent, poly(*N*-vinyl pyrrolidone) (PVP) as a tackifier and glycerol (GLY) as a plasticizer. The prepared gels can be applied to the skin by a coating method and *in situ* form very thin and transparent films with good performance, comfortable feel and cosmetic attractiveness. The key properties of the bioadhesive films produced from the hybrid gels were investigated and the results showed that the incorporation of appropriate GPTMS (GPTMS/(PVA + GPTMS) in the range of 20–30%) into the PVA matrix not only can significantly enhance mechanical strength and skin adhesion properties of the resultant film, but also can decrease the crystalline regions of PVA and hence facilitate the diffusion of water vapor and drug. Furthermore, the investigations into *in vivo* skin irritation suggested the films caused non-irritation to skin after topical application for 120 h. In conclusion, the bioadhesive films formed from organic–inorganic hybrid gels possessed very good qualities for application on the skin and may provide a promising formulation for TDDS, especially when the patient acceptability from an aesthetic perspective of the dosage form is a prime consideration.



## 1. Introduction

Transdermal drug delivery system (TDDS) can provide some desirable performances over conventional pharmaceutical dosage formulations, such as avoiding gut and hepatic first-pass metabolism, improving drug bioavailability, reducing dose frequency and stabilizing drug delivery profiles [1,2]. The current dosage formulations used for TDDS are mainly pressure sensitive adhesive patches, ointments and creams [3,4]. However, their performances are currently far from the optimum. For example, the transdermal patches often trigger several questions, such as skin irritation due to their occlusive properties preventing the permeation of water vapour from the skin surface, intense pain when peeled off from skin and difficulties for the preparation [5]. The ointments and creams are usually comfortable to wear but may leave a sticky or greasy feel after application [4]. Therefore, the search for alternatives to the conventional forms is reasonable in order to reduce skin irritation, improve skin adhesion properties, enhance the drug release and increase the patient acceptability from an aesthetic perspective. Because of their peculiar rheological behavior, polymeric gels are beneficial in terms of ease of preparation, ease of application, adhesion to the application surface and ability to deliver a wide variety of drugs [6]. Furthermore, the development of TDDS formulations recently has been focused on employing several polymer gels as a film-forming agent [7–12], whose administration typically involves coating a dose on the arms, shoulders, abdomen or internal parts of the thighs to fabricate a bioadhesive thin film on the skin surface. Compared with transdermal patches, ointments and creams, the innovative bioadhesive films represent an improvement because they offer more dosage flexibility and ease of use, less irritation potential, better cosmetic appearance and higher simplicity of manufacture, as well as do not leave greasy feeling on application site [13–15].

Due to their numerous favorable characteristics, specifically the excellent film-forming properties, processability, biocompatibility, non-toxicity, remarkable hydrophilicity and chemical resistance [16], films derived from PVA film-forming gels recently have attracted great attention and have been most widely used for pharmaceutical purposes [17–19], including dialysis membranes, wound dressing, artificial skin and transdermal drug delivery. Extensive research efforts on PVA-based bioadhesive film as a new platform have been carried out by Padula and his coworkers [20,21], which has demonstrated that the PVA-based film may be a promising vehicle for TDDS. However, several factors limit the use of PVA materials in TDDS. For example, the extreme water sensitivity and swelling capacity upon hydration of PVA lead to instability of its physiochemical properties. This feature makes it

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unsuitable for TDDS as the formulation applied on the skin surface must be able to maintain a stable adhesion after exposure to water or excessive perspiration. Furthermore, it is well known that PVA is a glassy, semi-crystalline polymer due to strong hydrogen bonds between the hydroxyl groups, and the crystalline regions of PVA are impermeable to drug diffusion [22]. PVA with relatively high glass transition temperature used for film formation is brittle at room temperature, leading to collapse of the PVA film after drying and exfoliation from the skin. Moreover, it is more restrictive that traditional PVA gels as the film-forming agent for TDDS are easy to rub off by clothes or movement due to their poor mechanical properties and deficient skin adhesions [23,24]. Additionally, the unsatisfactory film-forming time and inferior durability of PVA gels reduce the patient's compliance. Consequently, the properties of PVA and PVA gels need to be improved further in order to meet the strict demand in performance for TDDS application.

In the past 20 years, a steadily increasing attention has been paid to organic–inorganic hybrid gels due to a wide range of potential applications. Organic–inorganic hybrid film-forming agents offer an opportunity to combine the film-forming properties of a polymer and the stability of an inorganic compound to fabricate highly functional materials [25]. Many researches have reported that introduction of organosilicon into PVA and formation of organic–inorganic hybrid materials can improve mechanical properties and increase permeability [25–28]. Furthermore, the results indicated that appropriate selection of silica-modifying agent with sufficient hydrophilicity and ideal structure was crucial to obtain desirable attributes. The γ-(glycidoxypropyl)trimethoxysilane (GPTMS) is one of the most widely used agents because of possessing both an organically modified alkoxide moiety with an epoxy ring and trimethoxysilane groups that can easily cross-link with PVA chains. Furthermore, GPTMS has been used to produce PVA-silica hybrid films with improved permeability and biocompatibility in the field of separation processes, pervaporation and tissue engineering scaffold [26–29]. Therefore, the development of a novel organic–inorganic hybrid films for TDDS by combining the excellent properties of PVA and GPTMS is feasible. However, to the best of our knowledge, PVA-silica hybrid films used in TDDS have not been reported.

In the present work, an organic–inorganic hybrid film-forming gel was developed for TDDS using PVA as the matrix, GPTMS as the modifying agent, poly(*N*-vinyl pyrrolidone) (PVP) as the tackifier and glycerol (GLY) as the plasticizer. The hybrid film-forming gel can be directly coated on the surface of skin and form *in situ* a thin and bioadhesive film with an aesthetically pleasing, clear, transparent appearance and without any greasy feeling. The aim of this study was to evaluate several key properties for the resultant films daily use on the skin, including mechanical properties, skin adhesion properties and water vapor permeability. Moreover, the resultant films were also characterized by FT-IR, DSC, XRD and SEM. In addition, release characteristics of drug from the resultant films were studied using hydrophilic 5-fluorouracil (5-FU) and hydrophobic ibuprofen (IBU) as the model drugs. Additionally, the skin irritation and adherence of the hybrid films were also studied *in vivo* on living skin in human subjects, which could be valuable for the further development of this novel dosage form for TDDS.

## 2. Materials and methods

### 2.1. Materials

Poly(vinyl alcohol) (PVA) with a degree of hydrolysis of 85% and an average degree of polymerization of 1750 ± 50, which was used as the organic film-forming component, was supplied by Damao Chemical Co., Ltd. (Tianjin, China). γ-(Glycidoxypropyl)trimethoxysilane (GPTMS), which was used as the silica-modifying agent, was purchased from Nanjing Crompton Shuguang Organosilicon Specialties Group Co., Ltd. (Nanjing, China). Poly(*N*-vinyl pyrrolidone) (PVP) (K30, $M_n \approx 50{,}000$ g/mol) was the production of BASF ((Ludwigshafen, Germany). D,L-Lactic acid (88 wt% aqueous solution) was obtained from National Starch and Chemical Company (USA). Glycerol was obtained from Beijing Fangcao Pharmaceutic Company (Beijing, China). 5-Fluorouracil (5-FU, $M_n = 130.08$ g/mol, Log $K_{octanol/water} = -0.86$) and ibuprofen (IBU, $M_n = 206.27$ g/mol, Log $K_{octanol/water} = 3.94$) were supplied by Pharmaceutical Factory of Juhua Company (Tianjin, China). Cellulose dialysis membrane (100 μm thickness and 0.01 μm pore size) was procured from Shuoguang Science Instruments Co., Ltd. (Shanghai, China), and the other chemicals were analytical grade and used as received.

### 2.2. Preparation of organic–inorganic hybrid film-forming gels

The organic–inorganic hybrid gel was prepared via *in situ* sol–gel process according to a method modified from a prior study [29]. The possible scheme for the preparation of PVA–GPTMS–PVP–GLY film-forming gel was shown in Fig. 1. A weighed amount of PVA powder was dissolved in distilled water at 90 °C under reflux and stirring for 2 h to prepare a homogeneous PVA solution at a fixed concentration of 30 wt%. The hot solution was then filtered using the stainless steel sieve, and then, a certain amount of GPTMS and 2 mL of D,L-lactic acid catalyst were added to the filtrate to *in situ* initiate the cross-linking reaction. GPTMS was used as the modifying agent at various cross-linking ratios in order to investigate the effect of cross-linking ratio on mechanical properties, adhesion strength and the drug diffusion characteristics of the resultant films. The mixed solution was gently stirred for 12 h at room temperature. Additionally, the solution of 5-FU or IBU in glycerol alone was prepared. Subsequently, 0.5 g PVP and 9.5 g glycerol with or without drug were added into the aforementioned mixed solution containing 10 g PVA–GPTMS. The model drug was loaded at 5 wt% (based on the weight of PVA–GPTMS). Finally, the mixture was stirred slowly for 4 h at room temperature and left overnight to remove the entrapped air. The ultimate jellified gel was stored in glass vials sealed tightly with a siliconized rubber plug and an aluminum cap.

### 2.3. Bioadhesive and mechanical properties of organic–inorganic hybrid films

#### 2.3.1. Viscosity measurements

A viscometer (Brookfield DV-II + Pro programmable viscometer, USA) was used to measure the viscosities of the hybrid gels. The spindle was rotated at 10 rpm. Samples of the gels were to settle over 30 min at the assay temperature (32 °C) before the measurements were taken. A mean value of three specimens was taken.

#### 2.3.2. Peel test on skin

The peel adhesion test was conducted according to a method modified from the previous studies [30,31]. These tests were performed *in vivo* on the inner surface of the right forearm of 10 healthy volunteers (five men and five women, aged 20–28 years, 45–78 kg), participated in the study after signing a written consent. All volunteers were recruited from the School of Chemical Engineering and Technology, Tianjin University. Various formulations of film-forming gels were coated on the inner surface of the right forearm of 10 volunteers as previously described with a rectangular mold (2.5 × 5 $cm^2$, thickness = 0.5 mm) at room temperature. After acclimation for 10 min or 1 h, in order to eliminate the influence of elongation of hybrid film during the peeling

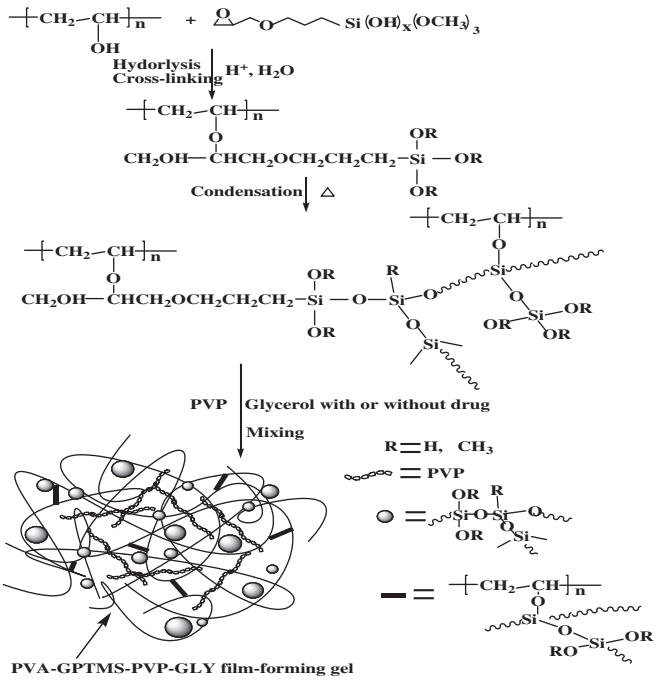



**Fig. 1.** Scheme for the preparation of PVA–GPTMS–PVP–GLY film-forming gel.

experiments, the air-exposed face of the film was coated a backing layer using an adhesive tape (cellophane) that was inextensible but flexible. Subsequently, the peeling force was measured with Testometric AX M350-10KN materials testing machine (Testometric Company, Germany) at a stripping angle of 90° and a stripping speed of 10 mm/min. The force required to detach the attached film from the forearm skin was used to represent the magnitude of bioadhesive force of the tested film specimen. Three specimens were tested for each sample.

### 2.3.3. Mechanical properties

In order to evaluate the mechanical properties, various formulations of film-forming gels were coated on a Teflon plate in a rectangular mold ($2.5 \times 5$ cm$^2$, thickness = 0.5 mm) in a dust-free atmosphere at room temperature. The films were allowed to dry at 40 °C for about 72 h, and the completely dried films were subsequently peeled off. The film was cut in the direction of machine flow into strips of $1 \times 3$ cm$^2$ size. Each strip was measured by a micrometer (GuoHua, China) for thickness at five different points along the length prior to testing. The thickness of final dry films was about 0.3 ± 0.1 mm. And then, the sample was carefully placed between two vertical grips of the tester that were covered with a silicon gum to prevent slippage of the films during the test. Mechanical tests including break stress and strain of all samples were performed at room temperature using a Testometric AX M350-10KN materials testing machine (Testometric Company, Germany) with an upward driven speed of 10 mm/min until the rupture occurred.

## 2.4. Water vapor permeability of organic–inorganic hybrid films

The water vapor permeability (WVP) was investigated according to a method modified from the British Pharmacopoeia [32]. Films used in this experiment were prepared according to the method described above in Section 2.3.3. Circular samples with a diameter of 2.0 cm were cut from the dry film sheets with a scalpel. Twenty-milliliter glass vials with an opening of 1.5 cm diameter ($A$ = 1.77 cm$^2$) were filled with approximately 10 g of distilled water, and the vials were weighed with an analytical balance before being sealed. The vials were then placed into a test chamber after they were covered with the circular film samples and sealed tightly with polytetrafluoroethylene swathe. The inside environment of the test chamber was kept at 37 °C and a relative humidity of 65%. They were kept for 24 h and weighed at predetermined intervals after removal from the test chamber for 1 h. The WVP is given by the following Eq. (1):

$$WVP = W/(A \times t) \quad (1)$$

where $W$ (g) is the weight loss of the vials, and $A$ (m$^2$) is the effective area of the exposed samples as well as time $t$ (24 h). For each formulation, the mean value of five repeated samples and the standard deviation were calculated. Controls for this experiment were vials without film samples which represented 100% water vapor permeability.

## 2.5. Characterizations of organic–inorganic hybrid films

Differential scanning calorimetry (DSC) was carried out using TA Instrument's DSC 2920 (TA Instrument, USA) with samples of about 10 mg sealed in aluminum pans under nitrogen atmosphere. The samples were first heated at a rate of 10 °C/min from 20 °C to 200 °C and kept there for 10 min in order to erase all thermal history, subsequently cooled down to −50 °C at a rate of 20 °C/min. The second heating scan from −50 °C to 200 °C at 10 °C/min was applied to assess the glass transition temperature. Fourier transform infrared spectroscopy (FT-IR) was carried out using KBr disks in the region of 4000–500 cm$^{-1}$ using BIO-RAD FT-IR 3000 (BIO-RAD Company, USA). The morphology of the film samples was analyzed through scanning electron microscopy (SEM). The dry films were gold coated to about 5 μm thickness using an IB-2 coater unit under a high vacuum. After that, SEM of films was performed on a Philips XL-30M scanning electron microscope instrument. The crystal states of film were observed by wide-angle X-ray diffraction (XRD) with graphite-filtered Co Kα radiation using an X-diffractometer (X' Pert, Holland). All the samples were measured at 20 mA and 45 kV with the scan range of 3–60° and the scan interval of 0.02°.

## 2.6. In vitro release study

The release of drug from different films through cellulose dialysis membrane as the diffusion barrier was examined using a modified Franz-type diffusion cell (1.65 cm$^2$ in area and 17 mL in receptor cell volume, Shishin Technology Co. Ltd., China). Films used in this experiment were prepared in the light of the method in Section 2.3.3. Circular samples with a diameter of 1.5 cm were cut from the dry film sheets with a scalpel and then were mounted on the diffusion barrier in the donor compartment. After acclimation for 1 h, the receptor compartments were filled with phosphate buffered saline (PBS, pH 7.4), containing 0.02% w/v of sodium azide to retard microbial growth. The solution in the receptor compartment was thermoregulated with a water bath at 37 ± 0.5 °C and stirred with a small magnetic bar. Samples (2 mL) were withdrawn at 2, 4, 8, 12, 16 and 24 h. Subsequently, the receptor compartment was replenished to its marked volumes with fresh buffer solution. Addition of solution to the receptor compartment was performed with great care to avoid trapping air beneath the membrane samples. All experiments were performed in quadruplicate.

The amounts of drug in the receptor solution were measured by HPLC (Agillent1100, USA) using Krcmafsis (250 mm × 4 mm, 5 μm) C18 column according to our previous study [33]. The cumulative amounts of drugs (μg/cm$^2$) at each collection time were plotted against time (h), and linear regression of the steady state portion of the curve was used to estimate drug flux (μg/cm$^2$/h). All release

data were mean ± SD. Statistical significance was checked by Student's *t*-test and considered to be granted at $P < 0.05$, unless otherwise indicated.

### 2.7. Cumulative skin irritation and adherence study in human subjects

The formulations of film-forming gels with the best characteristics were selected for testing further cumulative skin irritation and adherence study in human subjects. These tests were conducted *in vivo* on the inner surface of the right forearm of 10 healthy volunteers mentioned above. The most important exclusion criteria were the presence of skin disease or contraindication to transdermal systems. All subjects gave written consent to participate in the study, and all of the human experiments were performed in accordance with the Guidelines of Tianjin Institute of Pharmaceutical Research, Tianjin, China.

The drug-free gels were coated into a thin film on a clean, dry area of the right forearm of individuals of test group at room temperature. The duration of study was 120 h at the same skin site for evaluating skin irritation of the resultant films. However, application of a test film was discontinued at a site if predefined serious reactions occurred at the site of repeated applications. Application at a different site was subsequently initiated. Subjects were asked to visit the trial centre at 12 h intervals when new forming-film gels were reapplied by trial personnel. At the first visit after 12 h, the adherence performance of film was evaluated immediately prior to removal of the film. Scores corresponded to the percentage of the film surface in contact with the skin according to a 5-point scale of FDA [34]. Immediately following removal of a film, the amount of adhesive remaining at the skin site, as well as the signs and symptoms of skin irritation, was examined. Scores of adhesive residue on site were graded on a 4-point scale of FDA, where 0 = none, 1 = light, 2 = medium, 3 = heavy. The application-site irritations were assessed according to a visual scoring scale at each visit [35,36]. The total mean irritation score (TMIS, summation of mean irritation score of erythema and edema) was used as an index of skin damage caused by the application of film-forming gel. The TMIS of less than 0.50 denotes no irritation, and the mean irritation score of 0.5–2 denotes mild irritation. The TMIS of 2–6 and the TMIS of more than 6 denote moderate irritation and severe irritation, respectively.

## 3. Results and discussion

### 3.1. Preparation of film-forming gel and its appearance on skin

In order to provide an alternative vehicle for TDDS, a new type of organic–inorganic hybrid film-forming gel composed of PVA, GPTMS, PVP and GLY was developed. The application and appearance of film-forming gel (PVA:GPTMS:PVP:GLY = 75:25:5:95) was coated on the inner surface of the right forearm of volunteer as previously mentioned at room temperature and shown in Fig. 2. As seen from Fig. 2a, the novel organic–inorganic hybrid film-forming gel was a colourless, transparent, jelly-like substance with good flexibility and adhesive property, which was easy to be coated on the skin surface and *in situ* formed a very thin and comfortable film with an aesthetical appearance. Moreover, Fig. 2b distinctly displayed that the viscid gel turned entirely into a solid film and adhered tightly with skin after acclimation for about 10 min. The resultant film can form a smooth hard outer-surface which may reduce the risk of polluting clothes or being rubbed off by clothes. As seen from Fig. 2c to f, it can also be found that the film can maintain satisfactory application performance for 6 h and still adhere on skin almost integrally even after application of 12 h. Especially, the novel film formed on skin was quite different from traditional ointments and creams. Apart from without any greasy feeling, the film formed from organic–inorganic materials not only can maintain suitable skin adhesive properties to ensure longtime dressing, but also have enough strength to resist abrasion. This result indicated that GPTMS can exert a significant influence on the physicochemical properties and application performances of the resultant film, which were studied and described as below.

### 3.2. Chemical structure and miscibility study

For the blend-type polymer gels, the structural properties and the unique functions were dependent on the miscibility, chemical structure and interaction between mixture components. PVA, PVP and GLY had excellent compatibility due to the well-known observation of PVA and PVP solubility in glycerol [37]. Therefore, the miscibility of PVP–GPTMS was one of the key factors to offer suitable viscoelasticity for TDDS application. The high transparency of the film in Fig. 2 indicated that there may be no macro-phase sep-

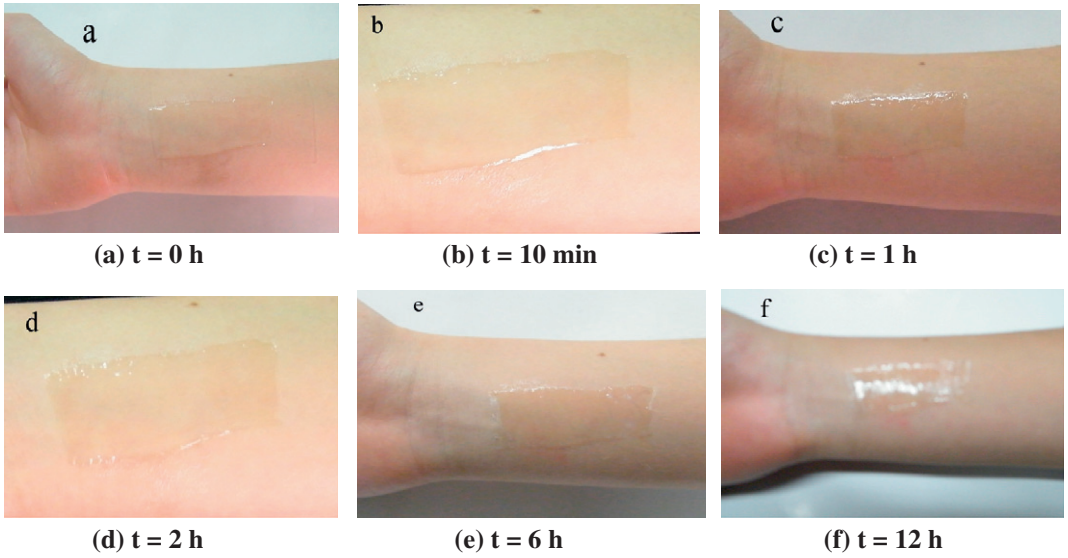



**Fig. 2.** Appearance photographs of PVA–GPTMS–PVP–GLY films on human forearm at different time; PVA:GPTMS:PVP:GLY = 75:25:5:95. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

aration occurring between the organic polymer and inorganic GPTMS. The good compatibility between polymeric component and inorganic GPTMS was attributed to the formation of covalent bonding, which was studied by FT-IR and DSC. The formation of PVA–GPTMS film prepared with different ratios of PVA and GPTMS was analyzed by FT-IR in Fig. 3. The band at 850 $cm^{-1}$ was associated with the stretching of Si—O—Si groups. The absorption peak at 920–950 $cm^{-1}$ was assigned to the stretching vibration of O—Si—O groups. The absorption peak at 1730 $cm^{-1}$, 2945 $cm^{-1}$ and a broad region around 3050–3700 $cm^{-1}$ can be assigned to the O—C=O stretching, the —$CH_2$— stretching, and the —O—H stretching, respectively. The FT-IR spectra in the range of 1040–1100 $cm^{-1}$ showed the existence of both Si—O—C and C—O—C groups, which indicated that the C—OH groups in PVA could react not only with the epoxy ring of GPTMS in acid conditions but also with the silanol Si—OH groups of GPTMS. The formation of Si—O—C groups and C—O—C groups will be in favor of better compatibility between organic and inorganic components and a better homogeneity of silica in PVA on the molecular scale [26].

DSC thermograms of the second heating scan of the PVA and PVA-based films were shown in Fig. 4. PVA showed a characteristic broad peak at around 70 °C, which represented the $T_g$ of PVA. The presence of a single $T_g$ in PVA–PVP–GLY can be taken as an indication of miscibility in this system. The miscibility of PVA, PVP and GLY could arise from hydrogen bond interactions between the amido or carbonyl groups of PVP and the hydroxyl of PVA and GLY. However, all DSC thermograms of PVA–GPTMS–PVP–GLY showed two glass transition temperature in the range of about 10–15 °C and about 74 to about 94 °C, which can imply all PVA–GPTMS–PVP–GLY samples exhibit the soft-hard segment micro-phase separation. The low and high $T_g$ may correspond to the soft and hard segments in the hybrid films, respectively. The flexible soft segments composed of uncross-linked PVA chain, PVP and abundant GLY primarily influenced the viscoelastic properties and low-temperature performance of the films, which can play an important role in skin adhesive properties. The hard segments due to the presence of cross-linked PVA–GPTMS and self-cross-linked GPTMS can provide enough mechanical strength and appropriate film-forming properties. Furthermore, it also can be seen from Fig. 4 that the high $T_g$ of PVA–GPTMS–PVP–GLY markedly increased with the considerable increase in GPTMS content, which can be attributed to the fact GPTMS can enhance the interactions between components and hence exert a significant influence on the hard segments. Contrarily, the low $T_g$ of PVA–GPTMS–PVP–GLY changed slightly with the change of composition, which may be due to the effect of abundant glycerol. In sum, it may be very suitable for TDDS due to the soft–hard segment micro-phase separation in the PVA–GPTMS–PVP–GLY, which can be further demonstrated from the bioadhesive and mechanical properties experiments.

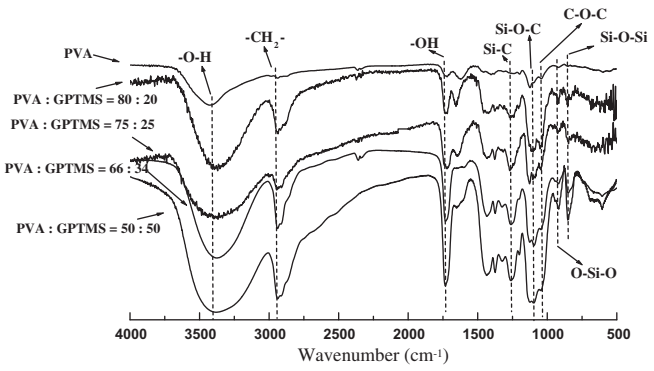



**Fig. 3.** FT-IR spectra of PVA and PVA–GPTMS hybrid films.

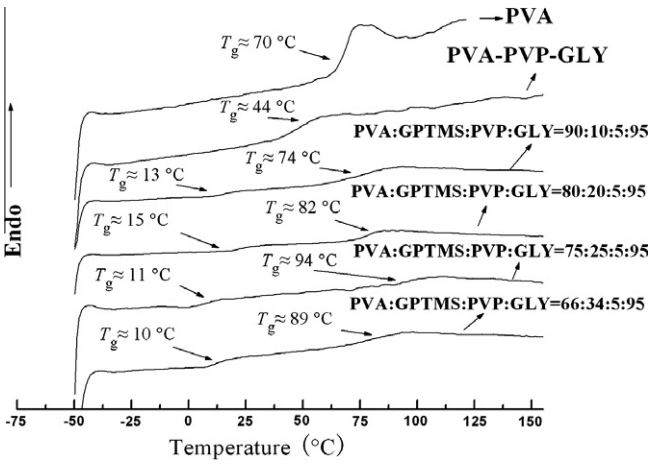



**Fig. 4.** DSC thermograms of the second heating scan of PVA and its hybrid films.

### 3.3. Bioadhesive and mechanical properties investigation

Bioadhesive is an essential property of film for a transdermal therapeutic product [29]. The peel adhesion tests of films arisen from the film-forming gel were conducted *in vivo* on the inner surface of the right forearm of some healthy volunteers according to a method modified from the previously studies [30,31], and the results were presented in Fig. 5. After acclimation for 10 min, 90° peel force of PVA–GPTMS and PVA–GPTMS–PVP–GLY films markedly increased with content of GPTMS increasing, probably as a result of that appropriate cross-linking of GPTMS can increase intermolecular force and strengthen the hydrogen bond action due to increasing amount of Si—O— in the system [38]. These factors together led to increasing their viscosity that was confirmed in Fig. 6. Moreover, it can also be seen from Figs. 5 and 6 that 90° peel force and viscosity of PVA–GPTMS were remarkably higher than PVA–GPTMS–PVP–GLY, which can be attributed to the dilution effect of plentiful glycerol [39]. However, after acclimation for 1 h, the data in Fig. 5 showed that 90° peel force of PVA–GPTMS sharply decreased whereas 90° peel force of PVA–GPTMS–PVP–GLY kept almost constant. In PVA–GPTMS films, the water as the unique plasticizer decreased rapidly due to being absorbed by skin and volatilization. As a result, the films lost its viscosity and flexi-

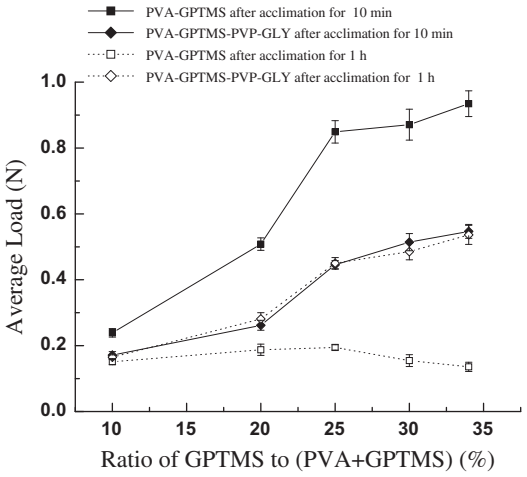



**Fig. 5.** 90° peel force of PVA–GPTMS and PVA–GPTMS–PVP–GLY films.

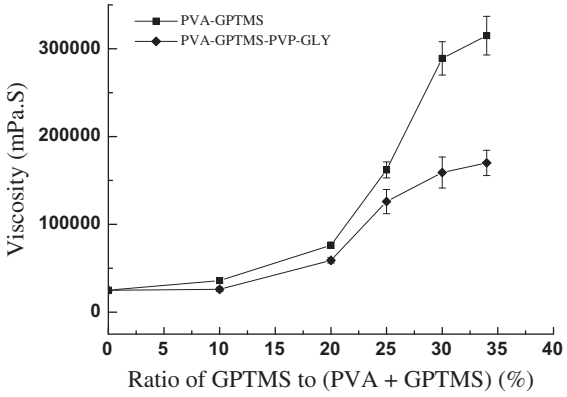



**Fig. 6.** Viscosity of PVA–GPTMS and PVA–GPTMS–PVP–GLY gels.

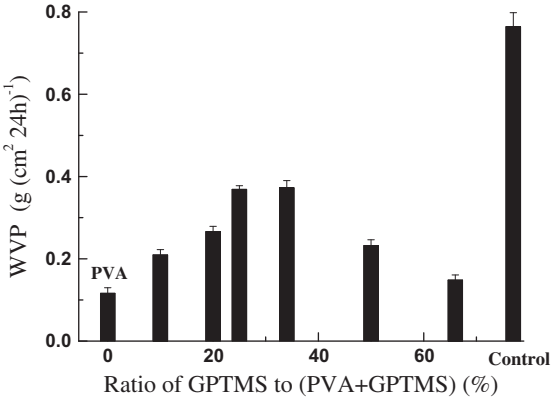



**Fig. 8.** WVP of PVA and its hybrid films.

bility, and thereby, 90° peel force sharply decreased. But for PVA–GPTMS–PVP–GLY, the existence of PVP and abundant GLY imparted to the film excellent skin adhesive properties to maintain longtime dressing. In sum, the addition of glycerol will form flexible soft segments and bring more free volume, which can improve the viscoelastic, adhesive and coating properties of PVA–GPTMS–PVP–GLY.

The final use of polymeric films for TDDS application strongly depended on their mechanical properties at room temperature. The representative stress–strain curves for PVA and its hybrid films with different GPTMS content were shown in Fig. 7. It can be seen that neat PVA film was a very brittle system with high level of the inner mechanical stresses due to strong crystallization. Moreover, GPTMS had a significant impact on mechanical properties of the resultant hybrid films. Compared with PVA–PVP–GLY, the stress of the hybrid films was markedly improved with increasing GPTMS content and the degree of elongation decreased with the increase in GPTMS, which apparently can be attributed to the strong interaction between PVA and silica. In sum, the addition of GPTMS into the bulk of PVA matrix was a feasible solution to improve toughness of the hybrid films in order to ensure excellent application performance.

### 3.4. Water vapour permeability analysis

It was well known that the occlusion of skin not only resulted in hydration but also altered other ecological factors and often caused severe skin irritation [4]. Therefore, a proper WVP of films was an important feature of a drug delivery system that was supposed to be worn on the skin for a prolonged period of time. The WVP of PVA and its hybrid films was assessed according to British Pharmacopoeia and showed in Fig. 8. The control represented unhindered water vapor permeation. The WVP of control value and PVA film was about 0.76 g $(cm^2\ 24\ h)^{-1}$ and 0.11 g $(cm^2\ 24\ h)^{-1}$, respectively. The relatively low WVP value of PVA film can ascribe to a large number of crystalline regions of PVA that are impermeable to water vapour diffusion. It also can be observed from Fig. 8 that the content of GPTMS had a significant impact on the WVP of PVA films. Moreover, a parabolic relationship was observed between the WVP of PVA films and the GPTMS content. The WVP values firstly increased with the increase in the GPTMS/(PVA + GPTMS) ratio from 0% to 34% and then rapidly decreased with a further increase in the content of GPTMS. GPTMS can effectively disorder the PVA chains and hence decrease the crystalline region of PVA, which therefore made water vapour diffusion easier. Nevertheless, the self-cross-linked reaction of GPTMS molecules proceeded preferentially at higher GPTMS content (GPTMS/(PVA + GPTMS) > 34%) [26], and thereby, the destruction of crystalline regions of PVA was depressed due to the decrease in cross-link reaction between PVA and GPTMS, which was demonstrated by the XRD and SEM in the following sections. In addition, the self-polycondensation reactions of GPTMS may result in the film more compact. As a result, the WVP rapidly decreased with a further increase in the content of GPTMS.

### 3.5. Crystalline properties characterization

The XRD was used to investigate the influence of GPTMS on the crystalline properties of the hybrid films, which was shown in Fig. 9. As seen, pure PVA film possessed distinctly higher crystalline intensity than its hybrid films, and all of results showed the main diffraction peaks were around $2\theta = 19°$ in the XRD patterns, which

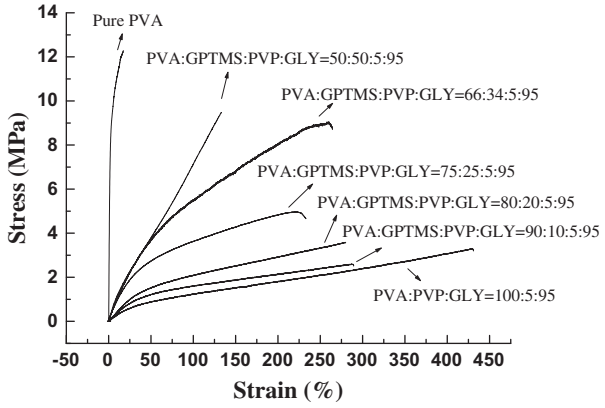



**Fig. 7.** Stress–strain curves of PVA and its hybrid films.

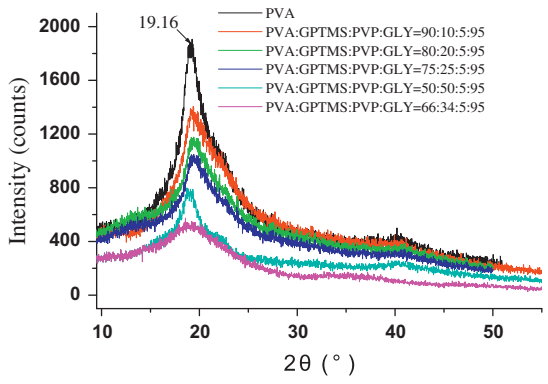
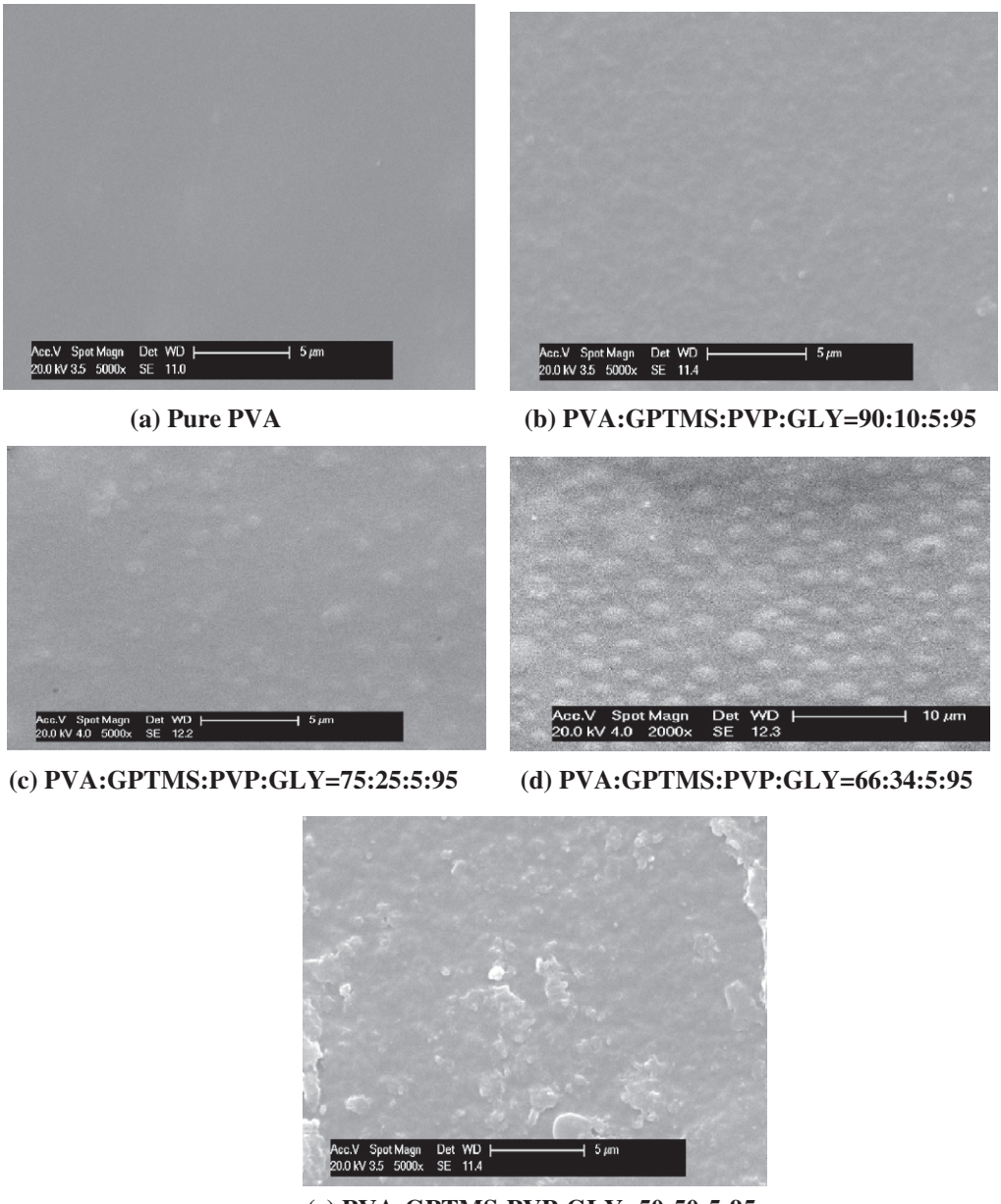



**Fig. 9.** XRD patterns of PVA and its hybrid films. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

can be ascribed to the crystalline regions of PVA due to strong hydrogen bonds between the hydroxyl groups. Furthermore, all peak intensities of PVA hybrid films decreased continuously with the increase in GPTMS/(PVA + GPTMS) ratio from 0% to 34%. Namely, there was a significant decrease in crystalline regions and increase in amorphous regions in the hybrid films, which can indicate that the introduction of GPTMS led to the destruction, to some extent, of the crystalline region of PVA film. Moreover, it can be seen that the peak intensity decreased with a further increase in the content of GPTMS, which may reflect the fact that there were the self-polycondensation reactions of GPTMS in the presence of an excessive amount of GPTMS, and thereby, the cross-link reactions between PVA and GPTMS were inhibited.

### 3.6. Surface morphology evaluation

SEM can provide direct visual evidence of the influence of GPTMS on surface morphology of the hybrid films. SEM photographs of surface sections of pure PVA and its hybrid films with different content of GPTMS are displayed in Fig. 10. From these micrographs, it can be seen that the surface of PVA film was both homogeneous and smooth. Moreover, the addition of GPTMS significantly affected the surface morphology. However, no visible phase separation between PVA and silica in all hybrid films can be observed. The hybrid film (PVA:GPTMS:PVP:GLY = 90:10:5:95) exhibited a homogeneous granular structure. Further increasing the content of GPTMS, the relatively homogeneous dispersion of silica microparticles within the matrix can be found. Furthermore, the number and size of silica microparticles increase with the increase in GPTMS. The presence of silica microparticles can be attributed to the reaction between PVA and the hydrolyzed silanol of GPTMS in the sol–gel process [39], which may play an important role in destroying regular crystalline arrangement of PVA chains and consequently decreasing the crystalline regions in PVA films. Moreover, the silica microparticles dispersed in the matrix can form hard segments in the PVA–GPTMS–PVP–GLY materials that




**(a) Pure PVA**

**(b) PVA:GPTMS:PVP:GLY=90:10:5:95**

**(c) PVA:GPTMS:PVP:GLY=75:25:5:95**

**(d) PVA:GPTMS:PVP:GLY=66:34:5:95**

**(e) PVA:GPTMS:PVP:GLY=50:50:5:95**

**Fig. 10.** SEM micrographs of surface sections of PVA and its hybrid films.

improve mechanical strength and film-forming properties. However, silica microparticles could not be clearly observed from the SEM photograph of the surface of hybrid film when GPTMS/(PVA + GPTMS) ratio is equal or greater than 50%. In addition, the surface morphology of hybrid film (PVA:GPTMS:PVP:GLY = 50:50:5:95) became rough and uneven, which was due to the polycondensation of excessive GPTMS leading to conglomeration and aggregation in the matrix. This conglomeration and aggregation may result in the film more compact that does not favor the diffusion of the drug molecule in the film.

### 3.7. In vitro release studies

The release of hydrophilic 5-FU and hydrophobic IBU in PVA and its hybrid films across cellulose dialysis membrane was shown in Fig. 11. It can be seen that all drug release profiles presented a fast initial burst release during the first 4 h, which may be due to rapid diffusion of drug on the surface of films. Subsequently, the formulation of films was observed to have a significant impact on drug release. For PVA and PVA–PVP–GLY film, a slow sustained release of 5-FU and IBU occurred, which may indicate that the diffusion process of drug within the film became very difficult due to the crystallization of PVA chain. However, the cumulative release of 5-FU and IBU from PVA–PVP–GLY film was found to be significantly higher than that from PVA film, which can conclude that addition of PVP and GLY enhanced the diffusion of drug. It was well known that the crystallization of drug in the matrix may cause a reduction in drug diffusion [40–42]. The PVP in film can improve the drug diffusion because the anti-nucleating effect of PVP can convert the crystalline drug into the amorphous state, which generally possessed a high thermodynamic activity that facilitated the diffusion of drug [42]. In addition, GLY may create a space and a large free volume within the film, leading to increasing molecular mobility and segmental relaxation and therefore enhancing drug diffusion [37,43]. As seen from Fig. 11, introduction of GPTMS can exert a strong impact on the drug diffusion through the hybrid films. Especially, the cumulative release of drug markedly increased when the GPTMS/(PVA + GPTMS) ratio is between 10% and 34% and then rapidly decreased with a further increasing GPTMS. The studies mentioned above have clearly shown that the appropriate amount of GPTMS can effectively increase the amorphous region of the matrix and accordingly enhance drug diffusion. On the contrary, the excessive GPTMS leading to self-cross-linked reaction of GPTMS made the film more compact and thereby made drug diffusion more difficult. It also can be seen from Fig. 11 that the cumulative release of hydrophilic 5-FU was much higher than hydrophobic IBU. Moreover, the hybrid film with GPTMS/(PVA + GPTMS) = 25% provided the best performance in terms of drug release of 5-FU, but other hybrid films (GPTMS/(PVA + GPTMS) = 10%, 25% and 34%) exhibited a similar effect on drug release of IBU. These results may be attributed to the existence of interactions between drug molecule and silica microparticles arisen from GPTMS within the hybrid films. Moreover, the interactions were strongly dependent on the physicochemical properties of drug, which will be further studied in our future work.

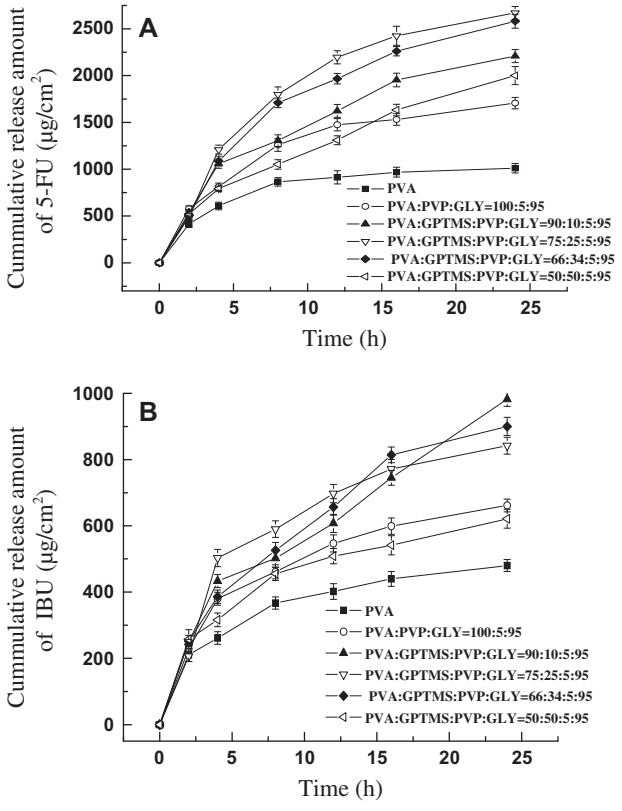



**Fig. 11.** Influence of GPTMS on the release of 5-FU (A) and IBU (B) in PVA and its hybrid films across cellulose dialysis membrane.

### 3.8. Skin irritation and application properties

The film-forming gels with the best characteristics were selected for further testing cumulative skin irritation. The results of the skin irritation study of the film (PVA:GPTMS:PVP:GLY = 75:25:5:95) were shown in Table 1. Based on the results, almost no skin irritation was observed in volunteers after skin dressing for 120 h, indicating that the PVA hybrid film was relatively safe to be used for TDDS during 120 h.

The application properties were investigated by the adherence study of PVA hybrid films in human subjects and shown in Fig. 12. The results indicated that film (PVA:GPTMS:PVP:GLY = 75:25:5:95) possessed excellent application properties. Almost all the tested samples were well adhered over 90% on the surface of skin during the experiment. However, the hybrid films with GPTMS/(PVA + GPTMS) = 10% and 34% were found to have some edges lifting off of the skin after application of 12 h. Especially for PVA:GPTMS:PVP:GLY = 66:34:5:95, the score of adherence

**Table 1**
Skin irritation scores of PVA–GPTMS–PVP–GLY hybrid film.

| Test substance[a] | Skin reaction[b] | Mean irritation score | | | | |
|---|---|---|---|---|---|---|
| | | 12 h | 24 h | 48 h | 72 h | 120 h |
| PVA:GPTMS:PVP:GLY = 75:25:5:95 | Erythema | 0 | 0 | 0.1 | 0.3 | 0.4 |
| | Edema | 0 | 0 | 0 | 0.1 | 0.1 |
| | TMIS | 0 | 0 | 0.1 | 0.4 | 0.5 |

[a] Test substance was the inner surface of the right forearm of 10 volunteers.
[b] For erythema and edema, the mean irritation score was the summation of each irritation score divided by the number of volunteers.

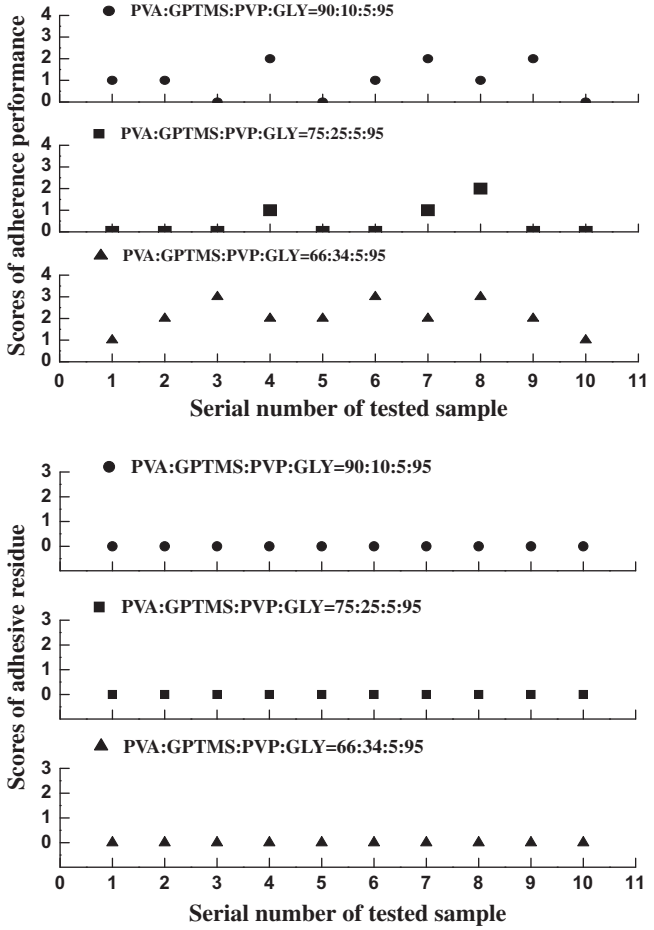



**Fig. 12.** Adherence performance and residue of PVA–GPTMS–PVP–GLY after application of 12 h.

performance was equal or greater than 2, which indicated that the film was unable to maintain long-term adhesion on the human skin. The research results in Figs. 5 and 6 have demonstrated that GPTMS can exert a positive impact on 90° peel force and viscosity of various PVA–GPTMS–PVP–GLY when the GPTMS/(PVA + GPTMS) ratio was in the range of 20–30%. Low content of GPTMS may not induce enough interactions between PVA chains. On the other hand, although high content of GPTMS can increase intermolecular force, high intermolecular force will lead to a high elastic modulus of the blend and an increase in the solid-like behavior and hence a decrease in tackiness and peel strength [44], especially when the content of plasticizer decreased sharply due to being absorbed by skin and volatilization after application of 12 h. It was worth pointing out that the plasticizer can exert a profound effect on the performance of hybrid gels and will be further studied in our future work. In conclusion, the PVA–GPTMS–PVP–GLY film with GPTMS/(PVA + GPTMS) ratio in the range of 20–30% possessed the most desirable application properties. In addition, the results in Fig. 12 indicated that, for all tested hybrid films, any adhesive residue on the surface of the skin was not observed, which can be due to the cross-linked effect of GPTMS.

## 4. Conclusions

A new type of organic–inorganic hybrid film-forming gel composed of PVA, GPTMS, PVP and GLY was used to develop a new formulation of TDDS. This novel film-forming gel was a colourless, transparent, jelly-like substance with good flexibility and adhesive property, which was easy to be coated on the skin surface and *in situ* forms a very thin and comfortable film with an aesthetical appearance but without any greasy feeling. In addition, the research results showed that the resultant film combined excellent film-forming properties of PVA, the crystallization inhibition function of PVP on loaded drug and the enhancement effect of GLY on drug permeation. More importantly, introduction of appropriate GPTMS (GPTMS/(PVA + GPTMS) ratio = 20–30%) into PVA matrix not only can significantly improve mechanical strength and skin adhesion properties of resultant film, but also can decrease the crystalline regions of PVA and hence facilitate the diffusion of drug and water. Furthermore, the skin irritation tests presented that the selected formulation produced no skin irritation after skin dressing of 120 h and was safe to be used in TDDS. In sum, the novel formulation of PVP–GPTMS–PVP–GLY may provide a feasible solution to the aforementioned problems of the use of polymer gel as a film-forming agent for TDDS.

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