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Development of Nonstick and Drug-Loaded Wound Dressing Based on the Hydrolytic Hydrophobic Poly(carboxybetaine) Ester Analogue

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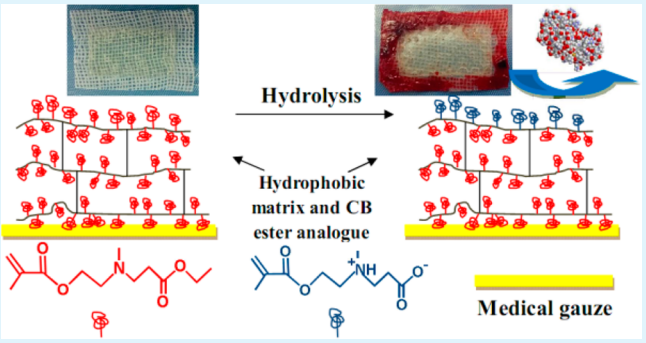
ABSTRACT: A novel biocompatible polymer is developed for antimicrobial and nonstick coatings of wound dressing. The polymer is formed by copolymerization of carboxybetaine ester analogue methacrylate (CB-ester) and small partial poly(ethylene glycol) methacrylate (PEGMA) for cross-linking by hexamethylene diisocyanate (HDI), which is highly resistant to nonspecific protein adsorption and mammalian cell attachment after a quick hydrolysis. A small hydrophobic drug, aspirin, can be incorporated into the new polymer and slowly released to inhibit microorganism growth while the new polymer shows very low cytotoxicity. Moreover, the wound dressing, the new polymer coated medical gauze, shows good mechanic properties, such as flexibility and strength, for medical application. After all, this new nonfouling polymer offers great potential for an antimicrobial wound dressing and other applications.



KEYWORDS: *nonstick, hydrolysis, nonfouling, carboxybetaine, wound dressing*

INTRODUCTION

Wound dressings, usually applied for first aid and post-surgical wound closure, provide physical support and protection from bacterial infection by creating a clean and moist environment.[1,2] A desirable function of wound care is nonstick removal. Johnson & Johnson Soothing Non-Stick Dressings are made with a unique petrolatum emulsion which prevents the dressing from sticking to a wound. Recently, Mi et al.[3] demonstrated a multifunctional wound dressing hydrogel with in situ forming capability and antimicrobial activity. Their nonstick wound dressings rely on the resistance to nonspecific protein adsorption and cell/bacterial adhesion of novel nonfouling materials, which is also critical for medical implants, tissue engineering, drug carriers, biosensors, and marine coatings.[4−7] Thus, nonfouling materials are very useful base materials for nonstick dressings.

Among different classes of nonfouling materials used in the biomedical field, poly(ethylene glycol) (PEG)-based materials[8,9] and zwitterionic-based materials have been widely used. However, PEG is readily subject to oxidation and loses its resistance in most biochemically relevant solutions.[10] In recent years, zwitterionic-based materials such as poly-(2-methacryloyloxyethyl phosphorylcholine) (pMPC),[11−13] poly-(sulfobetaine) (pSB),[14−16] and poly(carboxybetaine) (pCB)[17−20] have been considered to possess excellent biological compatibility, nonfouling properties, and higher stability than PEG. These nonfouling materials can form a physical and energetic barrier to prevent proteins adsorption through tightly binding with water molecules via electrostatic interactions.[21] Furthermore, the great versatility in selection of functional groups, such as carboxyl and various amine groups, as basic structure of nonfouling materials provides wide opportunities to realize new desired functions besides the resistance to nonspecific protein adsorption. Cheng et al.[22] demonstrated the switchable polymer coatings with self-sterilizing and nonfouling/biocompatible capabilities through the hydrolysis of poly(*N*,*N*-dimethyl-*N*-(ethoxycarbonylmethyl)-*N*-[2′-(methacryloyloxy)ethyl]-ammonium bromide). Our previous work has demonstrated that the silicone substrates containing CB ester analogue exhibited strong resistance to both nonspecific protein adsorption and bacterial adhesion via the interfacial hydrolysis of ester groups.[23] The hydrophobic matrix enables slow regeneration of the CB moieties and extension of the protein resistance lifetime of the silicone. Thus, zwitterionic-based materials are promising base materials for realizing multiple functions besides nonfouling property.

However, "Band-Aid"-like stable nonstick wound dressing, instead of hydrogel, is more desirable for daily usage. Here, we designed a CB ester analogue consisting of an esterified carboxybetaine (i.e. the carboxylate anion converted to the corresponding ester) and tertiary amine to obtain a hydrophobic base material with proper mechanism properties (Scheme 1). A copolymer of CB ester analogue and hydroxyl group containing poly(ethylene glycol) monomethacrylate was

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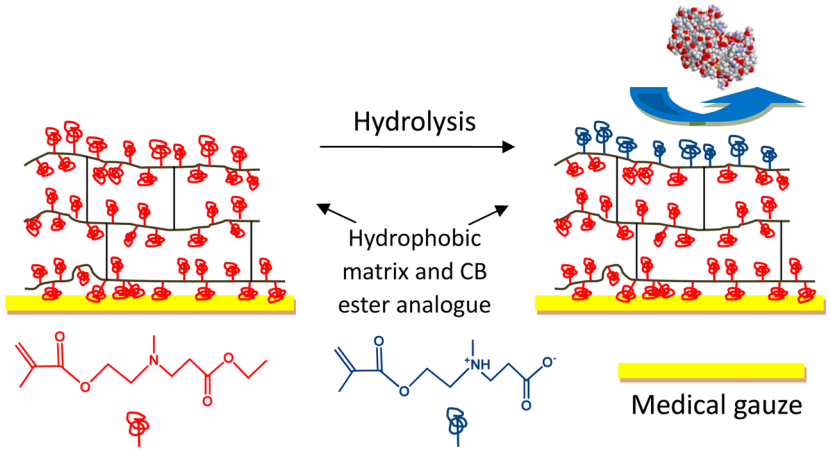
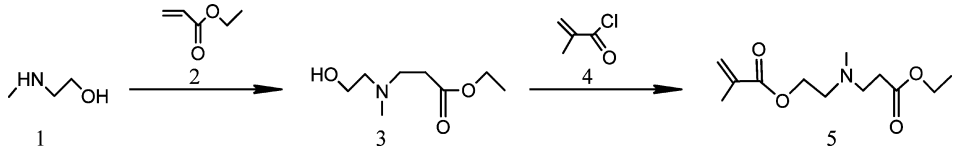
Scheme 1. High Resistance to Protein Adsorption and Mammalian Cell Attachment Is Obtained through Slow and Controlled Hydrolysis of CB Ester Analogue from the New Wound Dressing



Scheme 2. Synthesis of the CB Ester Analogue (Compound 5)



first synthesized as polyols. And then the polyols were cross-linked by a linear diisocyanate hard segment of hexamethylene diisocyanate (HDI) to improve mechanical properties. An antimicrobial model drug, aspirin, was also incorporated in this hydrophobic matrix. The final polymer could be utilized as thin polymer film independently or coatings on support film. Besides the low cytotoxicity and ease for utilization of this polymer coating, the resistance to nonspecific protein adsorption and mammalian cell attachment after a quick hydrolysis and also the capability of bacterial inhibition were investigated. Results suggested that this novel polymer coating is very promising for medical applications, especially nonstick wound dressing.

2. MATERIALS AND METHODS

2.1. Materials. Ethyl acrylate (≥99%), 2-(methylamino) ethanol (≥99%), methacryloyl chloride (≥95%), triethylamine (≥99.5%), 2,2′-azobis(2-methylpropionitrile) (AIBN, ≥98%), 2-hydroxyethyl methacrylate (HEMA, ≥98%), poly(ethylene glycol) monomethacrylate (PEGMA, M_n ~ 360), and hexamethylene diisocyanate (HDI, ≥99%) were purchased from Aladdin Reagents (Shanghai). Aspirin was purchased from Maya Reagent (Zhejiang). Horseradish peroxidase (HRP)-conjugated goat anti-human lgG(H + L) was purchased from Beijing Biosynthesis Biotechnology Co. Tetrahydrofuran (THF) and ethyl acetate were dried over molecular sieves 4A prior to use. All other chemicals were of reagent grade.

2.2. Synthesis of Carboxybetaine Ester Analogue. Ethyl acrylate was first dripped into 2-(methylamino) ethanol within 1−1.5 h at 0 °C. The mixture was stirred overnight at room temperature to form compound **3** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 4.14 (m, 1H), 3.60 (t, 2H), 2.76 (t, 2H), 2.56 (t, 2H), 2.49 (t, 2H), 2.29 (s, 3H), 1.27 (t, 3H).

Compound **3** was added to anhydrous tetrahydrofuran, followed by triethylamine addition. After adding methacryloyl chloride dropwise at 0 °C, the reaction was carried out overnight at room temperature. The mixture was then filtered, purified by alkaline alumina column, and concentrated in vacuo at 30°C. The resulting liquid was dissolved by ethyl acetate, extracted by a saturated sodium carbonate solution and then water, and dehydrated by anhydrous sodium sulfate, and the solvent was evaporated under rotary evaporation at 30 °C; a light yellow viscous liquid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.11 (m, 1H), 5.57 (m, 1H), 4.25 (t, 2H), 4.14 (q, 2H), 2.79 (t, 2H), 2.73 (t, 2H), 2.48 (t, 2H), 2.33 (s, 3H), 1.95 (s, 3H), 1.26 (t, 3H). The yield of compound **5** (Scheme 2) was ~90% with a purity of ~99% by ^{1}H NMR.

2.3. Preparation of Nonstick Polymer Films. The copolymer of CB ester analogue (92.5 mol.%) and PEGMA (7.5 mol %) was prepared by free radical solution polymerization using AIBN as initiator. Here, a mixture of CB ester analogue (9.25 mmol), PEGMA (0.75 mmol), and AIBN (0.25 mmol) was added to a flask. After the elimination of oxygen by bubbling with nitrogen gas, the reaction was carried out in THF (25 mL) at 65°C for 12 h. After rotary evaporation at 35°C, the product was precipitated into hexane to eliminate the unreacted monomers completely, and dried in a vacuum oven at 40°C for 24 h. The M_n and PDI values of copolymers determined by gel permeation chromatography (GPC) are listed in Table 1.

Table 1. Compositions of the Monomer Mixtures and M_n (GPC) for Various Copolymers

	monomer (mol %)	compd **5** (mol %)	M_n	PDI
polymer 1	HEMA 7.5	92.5	5800	2.02
polymer 2	PEGMA 5.0	95.0	4500	2.33
polymer 3	PEGMA 7.5	92.5	5400	2.26
polymer 4	PEGMA 15.0	85.0	5200	2.75

Two milliliters of ethyl acetate dissolved with the copolymer (1.0 g) and aspirin, with different feed compositions, followed by HDI addition (24.5μL, 0.55 times the molar weight of the hydroxyl group in copolymer) was casted into a customized Teflon mold. The casted solution was evaporated at 65 °C for 24 h. Then, the newly formed polymer film (thickness 0.25−0.5 mm) was taken from the mold and rinsed with ethanol to remove loosely bound compounds. In practice application, wound dressing was prepared by coating medical gauze with the new polymer. For comparison, polymer with HEMA instead of PEGMA was also prepared. The detailed compositions of polymers are listed in Table 1. The final film was cut into appropriate size and

then selectively hydrolyzed with 0.1 M NaOH at 37 °C for 0.25, 0.5, 1, 1.5, 3, and 6 h.

2.4. Gel Permeation Chromatography (GPC). The number and weight-average molecular weights (M_n and M_w) and molecular weight distribution (M_w/M_n) of copolymer were determined by using GPC (Schambeck SFD GmbH, RI2000, Germany) at 30°C. The mobile phase used was THF containing 0.5% triethylamine with a flow rate of 0.8 mL/min.

2.5. Attenuated Total Reflectance Infrared (ATR-IR) Analysis. ATR-IR characterization of the polymer was carried out using a Nicolet Nexus 670 FTIR spectrometer and a ZnSe crystal at a 45° angle of incidence.

2.6. Static Contact Angle Measurement. Static contact angles were measured using a Krüss DSA-10 contact angle goniometer (Hamburg) at room temperature and ambient humidity. All measurements were carried out by placing a 10 μL drop of liquid onto the surface of each fully cured polymer film using a 1000 μL screw-top syringe.

2.7. In Vitro Aspirin Release. An amount of 50 mg of aspirin was accurately weighed and located in a 50 mL volumetric flask and diluted with phosphate-buffered saline (PBS) as mother liquor. Then 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 mL of mother liquor were removed to 50 mL volumetric flasks with a pipette, diluted with PBS as standard solution. With PBS as the blank solution, the absorbance intensity of aspirin at 280 nm was next measured using a UV−vis spectrophotometer. Acetic acid (1.54%) was added to the test solution since aspirin would be hydrolyzed into salicylic acid and acetic acid. The standard curve with a linear range of 10−100 μg/mL was plotted, as shown in Figure 1. The obtained linear regression equation was $A = 0.0045c + 0.031$ (μg/mL) ($R^2 = 0.9983$).

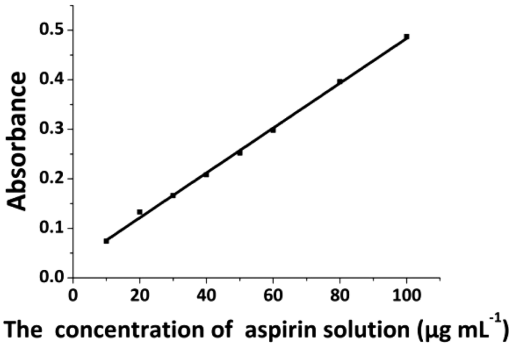


Figure 1. Standard curve of aspirin.

Aspirin-loaded polymer film disks (10 wt %; 6 mm diameter, 0.5 mm thickness) were soaked in 10 mL of PBS solution (37°C) with shaking at 200 rpm. Then 1 mL of PBS was removed for UV characterization at a desired time point and replaced by 1 mL of fresh PBS.

2.8. Protein Adsorption Measurement (ELISA). Nonspecific protein binding to the new polymer films and tissue culture polystyrene (TCPS) controls was determined by quantifying HRP-conjugated anti-IgG adsorption. First, the samples were incubated with 1 μg/mL anti-IgG for 1.5 h followed by five rinses with PBS. The films and TCPS controls were then removed and placed in 24-well plates. Next, 1 mL of 1 μg/mL *o*-phenylenediamine (OPD) in 0.1 M citrate−phosphate buffer, pH 5.0, containing 0.03% hydrogen peroxide was then added. Enzyme activity was stopped by adding an equal volume of 2 N H_2SO_4 after 15 min. The tangerine color (i.e. the relative protein adsorption) was measured at 492 nm.

2.9. Bacteria Growth Inhibition. *Escherichia coli* K12 single colonies were used to inoculate 5 mL of LB liquid media cultured at 37°C. Exponential phase bacteria was later harvested and diluted with fresh LB to appropriate concentration. Polymer film disks (6 mm diameter) were placed on the agar plates (80 mm in diameter) spread with 200 μL diluted bacteria culture. The inoculated plates were incubated at 37°C for 12 h. The antibacterial activities were evaluated by measuring the diameter of the bacteriostatic ring, which presented inhibition against the test bacteria. Each treatment was replicated three times.

2.10. HUVEC Cell Surface Attachment Assay. Polymer films (6 × 6 mm^2) and TCPS were placed individually in the wells of 24-well plates. After being irradiated with UV light for 30 min, HUVEC cells were seeded onto the samples at a concentration of 10^5 cells/mL in supplemented RPMI 1640 medium. Cells were allowed to grow for 24 h at 37°C, 5% CO_2, and 100% humidity, after which time the samples were photographed at 20× magnification on a Nikon Eclipse TE2000-U microscope. Each measurement had three replicate wells.

3. RESULT AND DISCUSSION

3.1. Surface Characterization of Nonstick Polymer Films. The chemical structure of the new polymer (polymer 3) was confirmed by ATR-IR as Figure 2 shown. Before

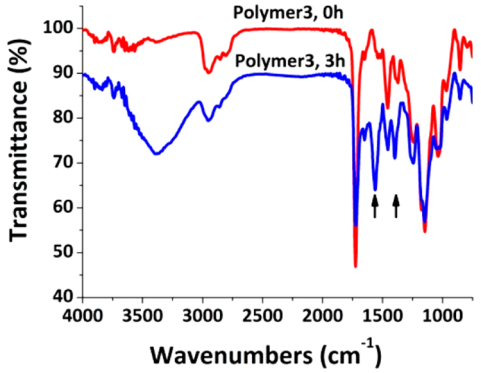


Figure 2. ATR-IR spectra of the polymer 3 before and after 3 h hydrolysis.

hydrolysis, specific absorption peaks were observed at 3372, 1726, and 1540 cm^{-1} mainly attributed to N−H stretching, C═O stretching, and N−H bending/C−N stretching of the urethane linkages. The peak at 2952 cm^{-1} was assigned to aliphatic $-CH_2$ groups of HDI. The strong peak at 1148 cm^{-1} represents the typical aliphatic ether functional group (C−O−C stretching) of PEG. Moreover, the peaks at 1650 and 1457 cm^{-1} corresponded to C═O (ester) and C−N groups of compound **5**, respectively. The results above clearly demonstrate the formation of urethane linkages and the incorporation of CB ester analogue through converting regular hydrophilic zwitterions into the hydrophobic precursor format to ensure high efficient cross-linking by HDI. The blue curve shows the spectrum of polymer after 3 h of hydrolysis in 0.1 M NaOH. The new peaks at 1561 and 1398 cm^{-1} were assigned to COO^- groups, indicating the hydrolysis of CB ester analogue and the formation of carboxybetaine groups. Zhang et al.[18] also demonstrated zwitterionic polymers formation through the preferential hydrolysis of polycarboxybetaine esters under basic conditions due to the high steric hindrance of the ester bond of methacrylate. Furthermore, an additional broad shoulder appears at 3393 cm $^{-1}$, probably due to an increase in hydration caused by the formation of hydrophilic zwitterionic polymer.

The surface hydrophobicity of the polymer film (polymer 3) is characterized by static water contact angle measurement. It can be seen from Figure 3, characteristically high contact angles were observed on the polymer film before hydrolysis (97.5 ± 1°). The hydrophilicity of the polymer surfaces was improved due to the increasing hydrolysis time and rising zwitterionic units, with an advancing angle of 26 ± 2° after 12 h of

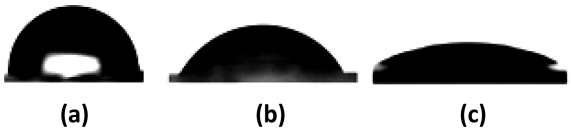


Figure 3. Typical advancing water contact angles of the new polymer films containing 92.5% CB ester analogue and 7.5% PEGMA (a) before hydrolysis using 0.1 M NaOH, (b) after 3 h hydrolysis, and (c) after 12 h hydrolysis. Here the advancing angles were (a) 97.5 ± 1°, (b) 66 ± 2°, and (c) 26 ± 2°.

hydrolysis. The results indicate that zwitterionic segments occurred near the surface of the polymer film, via the incorporation and hydrolysis of CB ester analogue. The increased hydrophilicity due to the zwitterionic polymer led to a significant improvement in nonfouling properties based on the water barrier theory.

3.2. Evaluation of Protein Adsorption on Nonstick Polymer Films. The adsorption of protein HRP-conjugated anti-IgG on these novel polymer films containing CB ester analogue and PEGMA before and after hydrolysis was evaluated by ELISA. The amount of protein adsorption on different films was determined by monitoring the increase in tangerine color intensity at 492 nm caused by the reaction of HRP with OPD, relative to films without hydrolysis. As shown in Figure 4b, after 3 h of hydrolysis, all films containing PEGMA showed a very low protein adsorption (<7%), compared with slightly higher protein adsorption of 18% on polymer 1 (HEMA 7.5%). Specifically, polymer 3 (PEGMA 7.5%) and polymer 4 (PEGMA 15%) can achieve an even lower fouling level of 6.0% and 1.5%, respectively. This is because PEGMA contains nearly six ethylene oxide units, which will also interact with water to create a hydration layer and provide some benefits for resisting protein adsorption. Thus, polymer 3 was selected as model film in the following experiments.

The protein adsorption versus hydrolysis time of polymer 3 was also studied. It can be seen from Figure 4a that polymer 3 could achieve a superlow fouling level after 0.25−1.0 h hydrolysis in 0.1M NaOH (pH 13). On the other hand, the protein adsorption maintains around 100% when polymer 3 is exposed in aqueous solution at pH 7. This indicated that the hydrolysis of the polymer is a necessary step to reach nonfouling property, suggesting that the nonfouling ability of polymer mainly results from the hydrolysis of CB ester analogue.

As shown, the hydrolysis rate of the polymer with 7.5% PEGMA was very rapid, almost complete hydrolysis of CB ester analogue on the surface within 0.5 h in 0.1 M NaOH. And its low-fouling ability could last 6 h or even longer, indicating that the polymer showed a slow and controlled rate of hydrolysis and that newly hydrolyzed zwitterionic CB ester analogue could reach the surface to maintain the low-fouling properties. That is because the urethane bond is better protected from hydrolysis than the ester bond in basic solution, which slowed down the degradation rate of these polymers in bulk format and led to the long-lasting protein resistance. Although the protein adsorption increased slightly after 1.5 h due to the possible hydrolysis of ester bond of methacrylate, there is no obvious damage to the resistance to protein adsorption after 6 h of hydrolysis. These results show that the new polymer films containing PEGMA and CB ester analogue are one of the excellent approaches for achieving great nonfouling ability.

3.3. In Vitro Aspirin Release. It is reported that aspirin could inhibit the growth of both Gram negative and Gram positive bacteria in vitro, such as *E. coli*[24] and *Staphylococcus aureus*.[25] Figure 5 shows the release profile of aspirin from the 7.5% PEGMA-based polymer film containing 10% aspirin in PBS at 37°C. Aspirin was released slowly to the environment at a reduced rate in the first 10 h, indicating that the new polymer has a significant slow-release effect upon aspirin dissolution. It will help to maintain the concentration of aspirin at the wound site, and ensure its antimicrobial effectiveness for a long time.

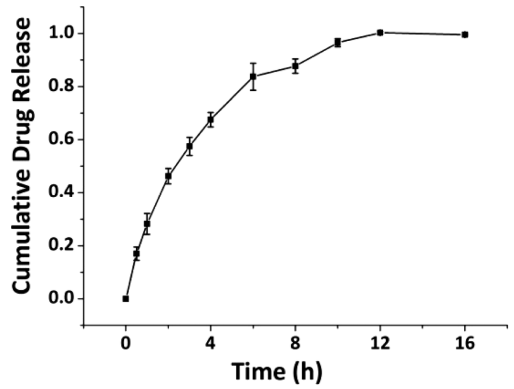


Figure 5. Release profile of aspirin from the 7.5% PEGMA-based polymer film containing 10% aspirin in PBS at 37°C as determined from UV detection.

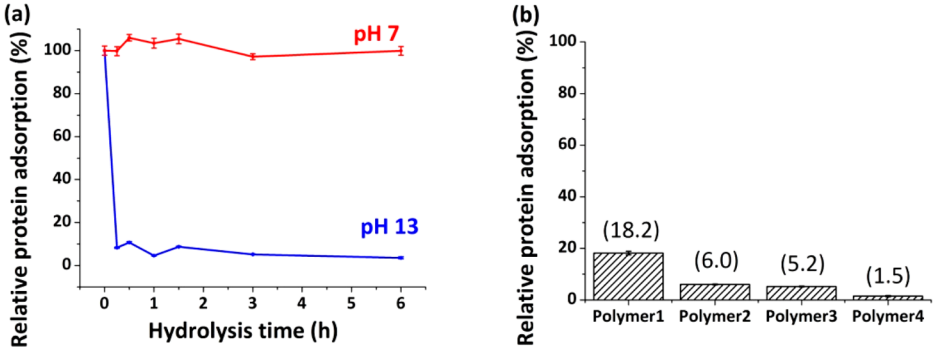


Figure 4. (a) Relative protein adsorption versus hydrolysis time for 7.5% PEGMA-based polymer film. (b) HRP-conjugated IgG adsorption on polymer films containing 7.5% HEMA (polymer 1), 5% PEGMA (polymer 2), 7.5% PEGMA (polymer 3), and 15% PEGMA (polymer 4), hydrolyzed for 3 h in 0.1 M NaOH. All data is normalized to IgG adsorption on 7.5% PEGMA-based polymer film without hydrolysis.

3.4. Antibacterial Activities. The bacteria growth inhibition assay by agar disc diffusion method was investigated to evaluate the antibacterial activity of the new polymer film against *E. coli* K12 strain to demonstrate the capability to reducing bacteria colonization and wound infection. As shown in Table 2, for the 7.5% PEGMA-based polymer film containing 0%, 5%, 10%, and 15% aspirin, the inhibition zone diameters were 6.6 ± 0.1, 9.7 ± 0.1, 10.7 ± 0.2, and 11.6 ± 0.2 mm, respectively. The results show that the material itself, without aspirin, exhibits merely no antibacterial effect. However, the effect became stronger with increasing aspirin content after adding aspirin in polymer matrix, which illustrates that the antimicrobial activity mainly comes from the aspirin release.

Table 2. Antibacterial Activities of the New Polymer Films Containing Aspirin

test polymer films	inhibition zone diameter (mm)[a]
polymer 3−0% aspirin	6.6 ± 0.1
polymer 3−5% aspirin	9.7 ± 0.1
polymer 3−10% aspirin	10.7 ± 0.2
polymer 3−15% aspirin	11.6 ± 0.2

[a]Diameter of inhibition zone including disc diameter of 6 mm.

3.5. Cell Adhesion on Nonstick Polymer Film Surfaces. The results of cell adhesion are shown in Figure 6. All hydrolyzed polymer films, with or without aspirin, exhibited no cell binding after 24 h HUVEC cell culture at 37°C (Figure 6a, c, and e). Figure 6b, d, and f shows cells attached at TCPS near the films. The cells exhibited flattened and spread morphology that is the sign of healthy cells. In general, the cell density near the 3 h hydrolyzed polymer films is the highest one, and the cell density near the 15 min hydrolyzed polymer films with additional 10% aspirin is the lowest one. These results indicate the high resistance to mammalian cell attachment and good cell compatibility or low cytotoxicity of the material, which is also in agreement with the observation by Zhang et al.[26] This good cell compatibility is mainly attributed to the reduced interaction with cell due to the nonfouling property and also to no toxic leaching of the polymer coating. Moreover, the additional aspirin only slightly affected the cell growth. Thus, the new polymer coating is able to kill microorganisms first, and prevent the attachment of microorganisms and cells.

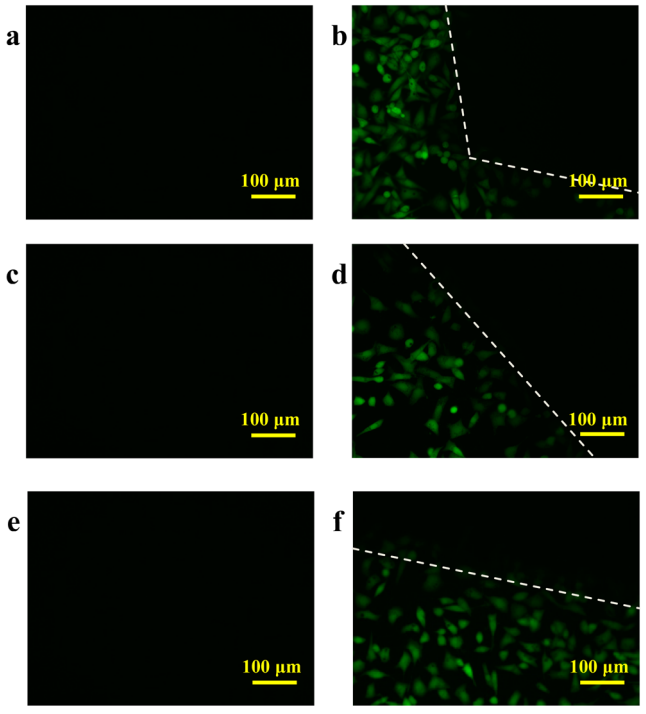


Figure 6. Representative microscopic images of HUVEC cells at a magnification of 20× after 24 h incubation with the new polymer films (a) without aspirin after 3 h hydrolysis, (b) cells near the film of (a), (c) with 10% aspirin after 15 min hydrolysis, (d) cells near the film of (c), (e) with 10% aspirin after 3 h hydrolysis, and (f) cells near the film of (e). The boundaries of films are marked with dotted lines.

The high resistance of the new wound dressings in blood has been investigated. The dressings were hydrolyzed by aqueous NaOH for 15 min, soaked in blood, and then followed by rinsing with PBS after the blood clotted. As expected, the dressing without the new polymer coating was covered by red blood cells and blood clots, while the coated area remained optically transparent and void of any red color, indicating that the new polymer coating could resist the attachment of red blood cells and blood clots (Figure 7). Since the attachment of red blood cells and blood clots is mainly caused by the adhesive proteins and platelets in blood cascade coagulation,[27] the resistance to red blood cells and blood clots will reflect the capability of the easy removal from wound site. Thus, this result also suggests the good nonstick capability of the new wound dressings.

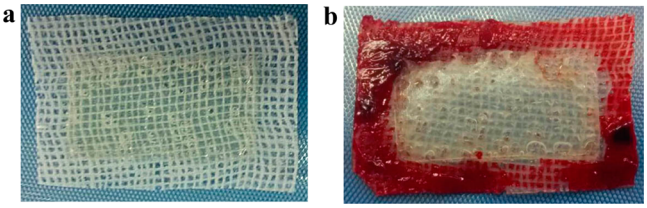


Figure 7. Optical images of the new wound dressings (a) before soaking in blood and (b) after soaking in blood.

Lastly, after 15 min facial hydrolysis, the internal hydrophobic and hard segments of HDI are physically adsorbed on the medical gauze by strong hydrophobic interactions. Moreover, the polymer layer on medical gauze is very stable even after 3 h hydrolysis in pH 13 solution. No polymer layer detachment is observed. This ensures the good mechanic properties of the wound dressing with the new polymer, such as flexibility and strength, for medical application.

4. CONCLUSION

In this work, we report the synthesis and characterization of a novel polymer containing CB ester analogue, PEG chains, aspirin and cross-linked by HDI. The interfacial hydrolysis of ester groups of the new polymer significantly enhances the surface hydration and enables effective resistance to nonspecific protein adsorption and HUVEC cell attachment. The additional aspirin released from the nonstick polymer films shows strong inhibition to *E. coli* K12 growth within 12 h. Moreover, the normal cell growth on TCPS around the films indicates its low cytotoxicity. All results indicate great potential of this nonfouling material for nonstick wound dressings.

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Notes
The authors declare no competing financial interest.

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