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Post-polymerization modification *via* the Biginelli reaction to prepare water-soluble polymer adhesives†

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Post-polymerization modification (PPM) has been widely applied to achieve new functional polymers by introducing functional groups to polymer precursors *via* efficient organic reactions. Most modification reactions were only studied as the coupling tools, and the unique functions stemming from the modification reactions were usually neglected. Here, a commercial monomer containing a β -keto-ester was used to prepare a water soluble copolymer precursor, and the tri-component Biginelli reaction has been utilized as the side chain modification approach to prepare a series of new polymers. Besides giving outstanding modification performance (rapid reaction rate, \sim 100% modification yield), the Biginelli linking group also possesses the new function of adhesion. As a result, when other adhesive functional groups were introduced through the Biginelli reaction, water soluble polymer adhesives comparable to commercial glues could be realized (\sim 7.55 MPa on a brass substrate). Moreover, the copolymer containing a phenylboronic acid group is not only an effective adhesive on different types of substrates (metal, plastic, bone), but also safe in the *in vivo* test, indicating the potential application of this polymer in bio-related fields. All these results suggested that the introduction of functional groups through a newly generated functional linkage can be simply realized by some multicomponent reactions, opening a new way to prepare functional polymers through the PPM strategy.

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Introduction

Post-polymerization modification (PPM) plays an important role in polymer chemistry to achieve functional polymers. By modifying the side groups of polymer precursors, new polymers with different properties/functions from their parents can be prepared. Some highly efficient organic reactions, such as copper-catalyzed azide–alkyne cycloaddition (CuAAC), thiolene/yne free-radical addition and so on,^{1–3} have been applied to prepare functional polymers by the PPM strategy. Most of these reactions have inspiring features including rapidness and robustness, high efficiency and atom economy, thus ensuring the nearly complete modification of polymer side chains to generate new functional polymers. Since Meier *et al.*

introduced the tricomponent Passerini reaction into polymer chemistry,^{4–6} more and more multicomponent reactions (MCRs) like Ugi,^{7–10} Biginelli,^{11–14} Hantzsch,^{15–17} Kabachnik–Fields reactions,^{18–21} thiolactone based MCRs^{22–24} and metal catalysed MCRs^{25–30} *etc.* have been successively exploited to prepare multicomponent polymers. Since MCRs are naturally rapid, highly efficient and atom economical, they have also been used as the coupling tools like other two-component reactions for PPM, and a series of polymers with multicomponent side groups have been successfully prepared.^{4,14,16,21} However, most of the abovementioned reactions were only regarded as a connection tool to link the desired functional groups on polymer backbones, and the specific functions of those linkages stemming from the coupling reactions have rarely been studied (Scheme 1a). Therefore, if the functionalities (similar to or different from the introduced functional groups) of PPM reactions can be explored, the function of the obtained polymer will be enhanced and the application areas of modified polymers might also be greatly expanded (Scheme 1b).

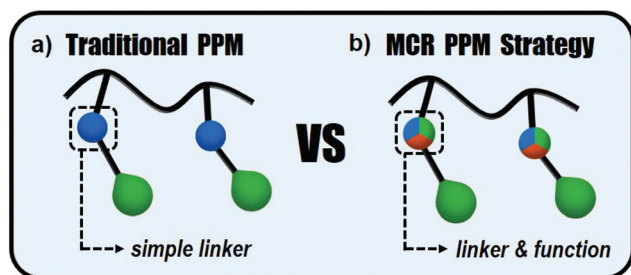
During our previous research, the Biginelli reaction, a tri-component reaction with a history of over 120 years attracted our attention. The Biginelli reaction is famous for the product dihydropyrimidin-2(1*H*)-ones (DHPMs), which have distinct

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Scheme 1 Comparison between (a) traditional and (b) MCR PPM strategies.

pharmacological properties.^{31–33} Our study of the Biginelli reaction focused on its features as a coupling reaction (modular, fast, efficient, atom economical, *etc.*) to synthesize polymers, and we found that the DHPM containing polymer can be used as a metal glue (tensile shear strength ~ 5.9 MPa) since the DHPM moieties in the polymer chain show a strong interaction with the metal surface while the small molecular DHPM does not show this interesting feature,¹³ suggesting that the polymer structure and the DHPM linkage supported each other to achieve a new functional polymer. Meier *et al.* also found that the polycondensates containing a DHPM moiety have high glass transition temperatures (T_g), expanding the application of the Biginelli reaction in polymer chemistry.³⁴

Encouraged by these previous research studies, we herein reported a multifunctional PPM strategy in which the modification reaction (the Biginelli reaction, for example) not only serves as a coupling tool, but also generates some specific functionalities to enhance the designed function of the target polymer. A commercially available monomer, (acetoacetoxy) ethyl methacrylate (AEMA) was copolymerized with poly(ethylene glycol) methacrylate (PEGMA) to obtain the copolymer (poly(AEMA-*co*-PEGMA)) by reversible addition–fragmentation chain transfer (RAFT) polymerization. RAFT polymerization was chosen due to its excellent reliability.^{35,36} Then, the copolymer was used as the precursor and different groups with potential adhesive capability, such as 4-hydroxyphenyl and 4-boronic acid phenyl, were implanted through the PPM strategy *via* the Biginelli reaction. The post-modified polymers were characterized by ¹H NMR and gel permeation chromatography (GPC), and the adhesive strengths of these polymers to different materials including metal, plastic, bone, *etc.* were tested, respectively, by using a universal testing machine. The adhesive strength data of these polymers were collected and analysed systematically, revealing the distinctively synergistic adhesion between DHPM and other functional groups.

Experimental section

Synthesis of poly(AEMA-*co*-PEGMA)

AEMA (5.14 g, 24 mmol), PEGMA-950 (11.4 g, 12 mmol), a chain transfer agent (CTA, 47 mg, 0.18 mmol) and AIBN (6 mg,

0.036 mmol) were charged into a Schlenk tube with 25 mL of toluene. The tube went through three cycles of freeze–pump–thaw to remove oxygen, then was sealed and kept in a 60 °C oil bath. After 24 h, the polymerization was quenched in an ice-water bath. The mixture was precipitated in diethyl ether 3 times, and then dried under vacuum to obtain the pure copolymer for further characterization and use.

PPM of poly(AEMA-*co*-PEGMA)

The post-polymerization modification of poly(AEMA-*co*-PEGMA) was carried out through the Biginelli reaction. Typically, poly(AEMA-*co*-PEGMA) (1.55 g), urea (264 mg, 4.4 mmol), benzaldehyde (350 mg, 3.3 mmol) and magnesium chloride (21 mg, 0.22 mmol) were dissolved in 5 mL of acetic acid, and then the mixture was stirred in a 100 °C oil bath for 4 h. The mixture was then dialyzed against methanol (MWCO: 3500) for 2 days to obtain the polymer (defined as PPM-1) after solvent evaporation (1.03 g, yield: 73.0%).

Through the same process, other polymers with different functional side chains were obtained by varying the aldehyde substrates, and named as PPM-2 (4-hydroxybenzaldehyde as the reactant) and PPM-3 (4-formylphenyl boronic acid as the reactant).

Tensile shear measurements

Preparation of specimens. Metal specimens (brass and aluminium) and polyethylene (PE) specimens were cut into uniform slides (100 × 10 × 0.1 mm). A bovine bone specimen was prepared in different sizes (25 × 20 × 0.4 mm) due to its weak physical strength. Metal specimens were polished with sandpaper (P800) and cleaned with acetone. PE specimens were sonicated in deionized water for 5 min and dried in air. The bovine bone specimen was polished with sandpaper (P2400) and cleaned with acetone prior to measurement.

Preparation of test joints. The aqueous solution of the modified polymer adhesive was prepared in deionized water (100 mg mL⁻¹), and then 15 μL of the solution was spread on two pieces of specimens separately. The coated specimens were overlapped and clamped together, and then kept in a 70 °C oven for 24 h (37 °C for bovine bone specimens).

The same conditions were applied to prepare test joints when commercial glues were used.

Tensile shear measurement procedure. The tensile shear strength was measured according to reported literature with slight modifications.³⁷ The overlap length was set as 10 mm, and the free crosshead speed was set to 2.0 mm min⁻¹. Ten samples were tested for each polymer adhesive, and the data are presented as mean ± standard deviation (SD).

Results and discussion

Side chain modification of poly(AEMA-*co*-PEGMA) with the Biginelli reaction

Through the Biginelli reaction, the side chain of the polymer precursor has been efficiently modified to generate new func-

tional polymers. Briefly, a random copolymer, poly(AEMA-PEGMA) ($M_n \sim 31\,000\text{ g mol}^{-1}$, PDI ~ 1.18), was synthesized through RAFT polymerization. The random copolymer contains the β -keto-ester group as the reactive side chain which was then modified through the Biginelli reaction in the presence of urea, and different aldehydes (MgCl₂ as the catalyst and acetic acid as the solvent) to link phenyl (PPM-1), 4-hydroxyphenyl (PPM-2) and 4-boronic acid phenyl (PPM-3) in the polymer structure *via* the DHPM group.

The ¹H NMR spectra of daughter polymers showed tremendous differences compared with the parent poly(AEMA-PEGMA) (Fig. 1b). According to the ¹H NMR spectrum (PPM-1 as an example), the characteristic peaks of the Biginelli structure, two CONH peaks (9.27 ppm and 7.73 ppm), CH (5.16 ppm) and the protons of the aromatic ring (7.10–7.40 ppm) could be clearly observed, while the methylene of the β -keto-ester group (3.62 ppm) disappeared thoroughly, indicating the complete Biginelli reaction and the successful side chain modification of poly(AEMA-PEGMA) (Fig. 1c).

From the integral ratio between the CH in the DHPM ring and the terminal methyl of PEGMA ($I_{5.16} : I_{3.23}$), the efficiency of the side chain modification can be calculated to be $\sim 100\%$. Moreover, the GPC trace of the modified polymer showed a narrow polydispersity index (PDI ~ 1.19) (Table S1, Fig S1[†]), indicating that the modification process only changed the side chain while leaving the polymer backbone intact. Similarly,

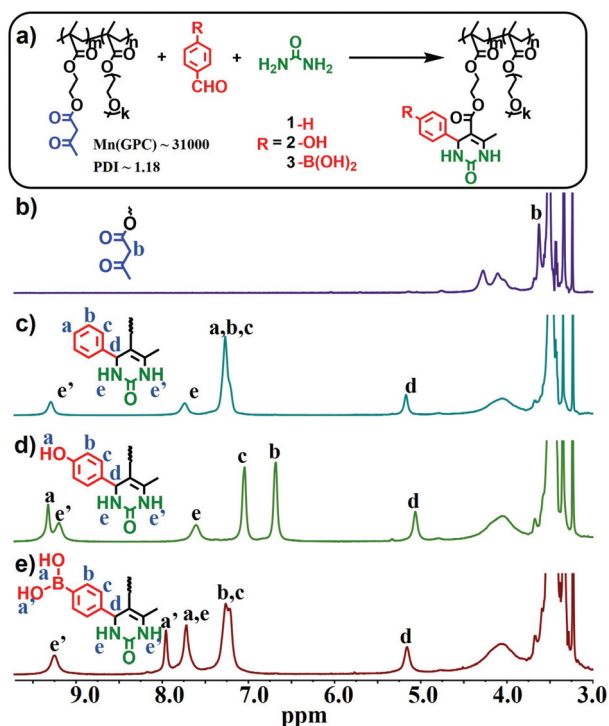


Fig. 1 (a) PPM of poly(AEMA-PEGMA) *via* the Biginelli reaction. Reaction conditions: [1,3-dione group]_{poly(AEMA-co-PEGMA)}/[benzaldehyde]/[urea]/[MgCl₂] = 1/1.5/2/0.1, acetic acid as the solvent, 100 °C, 3 h. ¹H NMR spectra (DMSO-d₆, 400 MHz, portion) of (b) poly(AEMA-co-PEGMA), (c) PPM-1, (d) PPM-2, and (e) PPM-3.

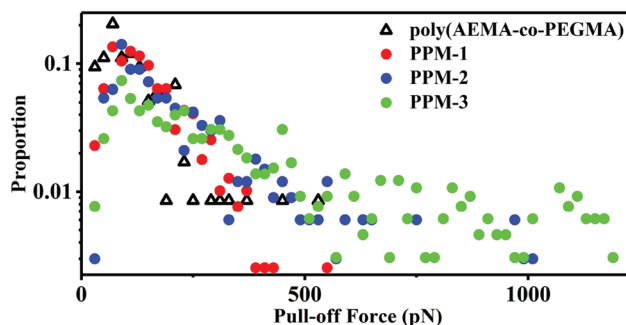


Fig. 2 The statistical analyses of the pull-off forces of poly(AEMA-co-PEGMA) and the modified polymers, respectively.

when other aldehydes were used as substrates, target polymers were smoothly obtained with a nearly complete modification efficiency (Fig. 2d, e and Table S1[†]), suggesting that the Biginelli reaction is an excellent approach to realize highly efficient PPM.

Metal bonding capacity of modified polymers

Polycondensates prepared by using the Biginelli reaction showed strong metal bonding ability due to the interesting interaction between the DHPM moiety and the metal surface.¹³ Thus, by using the Biginelli reaction as a simple and efficient modification method to introduce adhesive groups into the polymer structure, the thereof obtained polymers (PPMs) might have improved performance in bonding metal specimens.

To verify the interaction between the modified samples (PPM 1–3) and the metal surface at the molecular level, the modified polymers and poly(AEMA-PEGMA) (control polymer) were tested through Single-Molecule Force Spectroscopy (SMFS) (Fig. 2). The pull-off force of the parent poly(AEMA-PEGMA) was mainly distributed in the low force area ($<250\text{ pN}$), while its daughters PPM-1, PPM-2 and PPM-3 showed increased probability in the higher force area ($\sim 500\text{--}1000\text{ pN}$). PPM-1 stemming from benzaldehyde had stronger pull-off force than poly(AEMA-PEGMA), confirming the microscopic strong interaction between the DHPM moiety in the polymer structure and the metal surface. Meanwhile, PPM-2 and PPM-3 demonstrated clearly stronger pull-off force than PPM-1, suggesting that the introduced group and the newly generated group can cooperate to enhance the function of the polymer.

Subsequently, the detailed study of macroscopic bonding behaviour was performed. The metal bonding capability of the daughter polymers was tested following the typical procedure as below: both ends of the metal pieces (1 cm \times 1 cm, brass specimen as a model) were covered with the polymer solution (15 μL , 100 mg mL⁻¹), then two pieces of the metal were clamped and kept in an oven for a designed time. The glued metal pieces were fixed by the clamps of the universal testing machine (Fig. 3a). Consistent reverse tension was provided until the test joint broke, and the maximum tensile force before breaking was recorded. The influence of the curing time on the adhesive strength has been studied using PPM-2

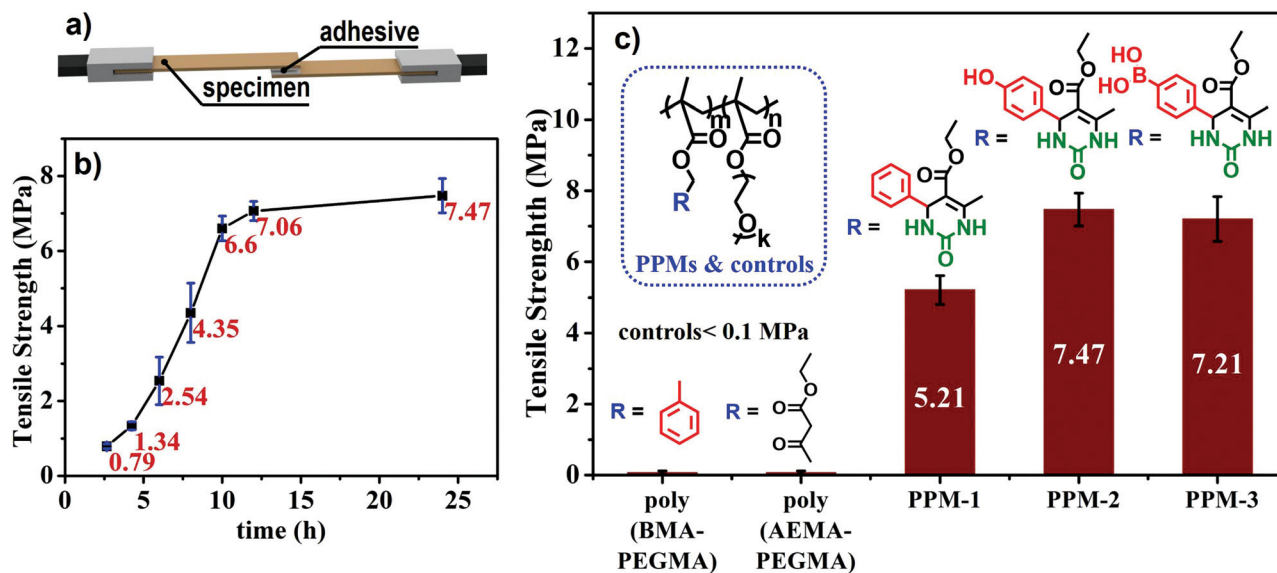


Fig. 3 (a) Schematic representation of the tensile shear measurement procedure; (b) kinetics study of the adhesive process (PPM-2, brass specimen, 5 parallel tests for each point); (c) tensile strength of poly(BMA-*co*-PEGMA), poly(AEMA-*co*-PEGMA) and PPMs (brass specimen, 10 parallel tests for each sample).

as the glue (Fig. 3b), and the bonding strength was found to gradually increase until a plateau (~ 7 MPa) was reached after around 12 h. Thus, the experiment time was set as 24 h to guarantee complete adhesion. All three modified polymers were tested and showed a strong sticking effect on brass specimens (Fig. 3c). In particular, PPM-1, which is modified with the phenyl group through the Biginelli reaction, showed a relatively high shear strength (~ 5.55 MPa), while the parent polymer poly(AEMA-PEGMA) showed weak bonding strength (Fig. 3c). Poly(benzyl methacrylate-*co*-PEGMA) (poly(BMA-*co*-PEGMA)) was also prepared and tested, and no clear metal sticking ability was observed, suggesting that the phenyl group offers no specific interactions with the metal surface (Fig. 3c). Therefore, the strong adhesion of PPM-1 should be attributed to the metal bonding capability of the DHPM moiety stemming from the Biginelli reaction. Meanwhile, compared with PPM-1, PPM-2 (containing the 4-hydroxyphenyl group) and PPM-3 (containing the 4-phenylboronic acid group) showed a higher bonding strength (Fig. 3c, ~ 7.47 MPa, 7.21 MPa), which might be attributed to the combined interaction of the introduced adhesive groups and the DHPM ring on the brass substrate, leading to the enhanced sticking effect of PPM-2 and PPM-3. Therefore, poly(AEMA-PEGMA) could be upgraded as a metal glue by the modification through the Biginelli reaction, and the adhesive effect could be further improved by introducing adhesive groups, suggesting the synergistic effect between the modification reaction and the introduced functional groups.

Bonding test using other substrates

To verify the versatility of these polymer-adhesives, the daughter polymers were used to stick different substrates including metals (brass and aluminium), plastic (PE), and biomaterial

(bovine bone). All the specimens were prepared and tested under the same conditions (quantity, overlap area, curing time, and curing temperature) except for bovine bone specimens (curing temperature: 37 °C) to imitate the biological environment. Some commercial glues such as poly(vinyl acetate), polyurethane and cyanoacrylate (Fig. 4, Table 1) were also tested using the same specimens under the same conditions to further evaluate the sticking effect of the modified polymers for their possible practical applications.

When metal samples were used, all daughter polymers showed strong sticking ability, and PPM-2 exhibited the strongest bonding strength (~ 7.47 MPa for brass, ~ 3.14 MPa for aluminium) (Fig. 4), similar to the performance of commercial glues (~ 7.95 MPa for brass, ~ 4.66 MPa for aluminium). The possible reason might be that the phenol moiety can form complexes with some metal/metal oxides and there is a possible self-crosslink group by oxidation.³⁸

All daughter polymers had weak sticking strength when PE specimens were tested; the strongest sticking strength is only 0.15 MPa by PPM-1 (Fig. 4, Table 1), which is attributed to the fact that a PE specimen has no polar functional group on its surface to interact with polymer adhesives. A similar phenomenon was also found when commercial glues were used, only 0.47 MPa was observed as the strongest bonding strength when the commercial cyanoacrylate glue was used (Fig. 4, Table 1).

When bovine bone specimens were tested, PPM-3 achieved the best outcome of ~ 5.58 MPa among the daughter polymers, which is even stronger than commercial poly(vinyl acetate) (~ 4.06 MPa) and cyanoacrylate (~ 5.57 MPa). The excellent performance of PPM-3 might be attributed to the interaction between the phenylboronic acid moiety and the biomolecules

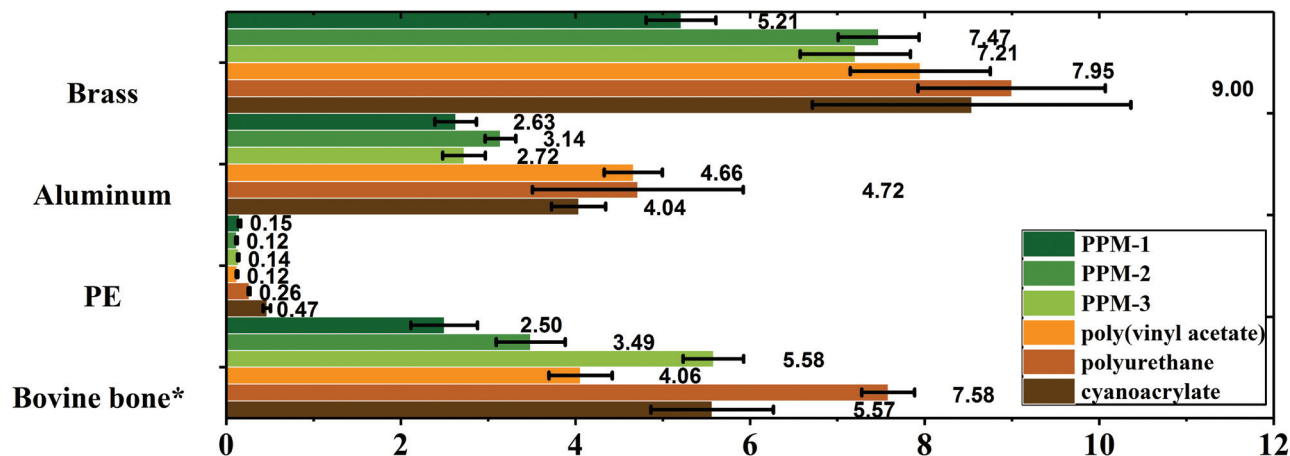


Fig. 4 Tensile strength of PPM 1–3 bonding different substrates compared to commercial glues. Each strength value was determined by performing 10 parallel tests. All tests were carried out at 70 °C for 24 h. *37 °C for bovine bone samples.

Table 1 Tensile strength of SCMPs bonding different substrates compared to commercial glues

	SCMP-1	SCMP-2	SCMP-3	Poly(vinyl acetate)	Polyurethane	Cyanoacrylate
Brass	5.21 ± 0.4	7.47 ± 0.46	7.21 ± 0.63	7.95 ± 0.8	9 ± 1.07	8.54 ± 1.82
Aluminum	2.63 ± 0.24	3.14 ± 0.17	2.72 ± 0.24	4.66 ± 0.33	4.72 ± 1.21	4.04 ± 0.31
PE	0.15 ± 0.01	0.12 ± 0.01	0.14 ± 0.01	0.12 ± 0.01	0.26 ± 0.01	0.47 ± 0.04
Bovine bone ^a	2.5 ± 0.38	3.49 ± 0.4	5.58 ± 0.35	4.06 ± 0.36	>7.58 ± 0.3	5.57 ± 0.7

^a 37 °C for bovine bone samples.

(glycoprotein, saccharide, protein, *etc.*) on the surface of bovine bone specimens.

Furthermore, the bio-safety of PPM-3 was tested. The *in vivo* tests were performed under the technical guidelines for the non-clinical study issued by CFDA, and authorized by the ethics committee of Cancer Hospital, Chinese Academy of Medical Science.

The PPM-3 solution (200 μL, 100 mg mL⁻¹) was injected into the hip of a nude mouse, and then the mouse was observed for 72 h (Fig. 5a). As the control, the other nude mice

were injected with the commercial cyanoacrylate glue (200 μL) and kept for the same time for observation (Fig. 5a'). In appearance, there is no sign of swelling and inflammation for both mice (Fig. 5a and a'), preliminarily indicating the safety of PPM-3 and the cyanoacrylate glue. However, after the removal of the skin, the commercial cyanoacrylate glue showed clear solidified residues in the muscle (Fig. 5b, right), while the PPM-3 solution left no visible residue (Fig. 5b, left). These results suggested that PPM-3 has excellent safety for bio-application and is easier to be cleaned up by organisms.

All the above results indicated that a polymer without a special functionality can gradually evolve from PPM as a bio-compatible glue which can even compete with commercial adhesives. The interesting adhesive properties of DHPM in the polymer structure offer a new candidate to design functional polymers for (bio)adhesion, resulting in the water-soluble and biocompatible PPM-3 as a potential bio-glue for clinical surgery.

Conclusions

A copolymer poly(AEMA-*co*-PEGMA) was synthesized and used as a precursor for PPM. The side chain (β-keto-ester) of the polymer precursor was modified through the tricomponent Biginelli reaction to introduce different functional groups. The robust Biginelli reaction ensured rapid and complete PPM.

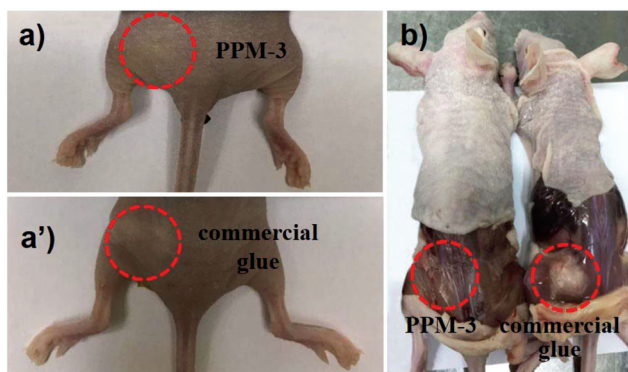


Fig. 5 Photos of nude mice at 72 h after injection of (a) PPM-3 solution (200 μL, 100 mg mL⁻¹) and (a') the commercial cyanoacrylate glue (200 μL); (b) PPM-3 solution (left) and the commercial glue (right) with skin resected.

Moreover, the Biginelli reaction also generated linkages possessing the unique function of adhesion which can be further strengthened by introducing functional groups. As a result, functional polymers which can glue different substrates have been developed, and some polymer samples can even compete with commercial glues or have the potential for applications in bio-fields.

The utilization of MCRs in polymer chemistry is becoming a vibrant branch and MCRs can form unique compounds with special physicochemical and pharmaceutical properties. The current research is only a preliminary attempt to develop new functional polymers through the PPM strategy *via* MCRs, and we believe a wider variety of polymers with interesting and unique properties/functions will be feasible when people look at the MCRs from the perspective of polymer chemistry.

Conflicts of interest

The authors declare no competing financial interests.

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