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A New Bioactive Polylactide-based Composite with High Mechanical Strength

Quanxiao Dong^{a,b,d,e}, Laurence C. Chow^c, Tongxin Wang^{a,b,*}, Stanislav A. Frukhtbeyn^c, Feng Wang^d, Mingshu Yang^{d,*}, and James W. Mitchell^a

^aCrest Center for Nanomaterials, College of Engineering, Howard University, Washington, DC 20059, USA

^bCollege of Dentistry, Howard University, Washington, DC 20059, USA

^cAmerican Dental Association Foundation, Dr. Anthony Volpe Research Center, National Institute of Standards and Technology, Gaithersburg, MD 20899, USA

^dCAS Key Laboratory of Engineering Plastics, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

^eBeijing Engineering Research Center of Architectural Functional Macromolecular Materials, Beijing Building Construction Research Institute, Co., Ltd., Beijing, 100039, China

Abstract

A new bioresorbable polylactide/calcium phosphate composite with improved mechanical strengths and a more basic filler, tetracalcium phosphate (TTCP), was prepared by melt compounding. N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEAPS) and pyromellitic dianhydride (PMDA) were used to improve the interfacial adhesion between TTCP and polylactide (PLA). While AEAPS improved the dispersion of TTCP in the matrix, PMDA might react with the terminal hydroxyl group of PLA and the amino group on the surface of AEAPS modified TTCP, which could further enhance the interfacial strength. The tensile strength was improved to 68.4 MPa for the PLA/TTCP-AEAPS composite from 51.5 MPa for the PLA/TTCP composite (20 wt% of TTCP). Dynamic mechanical analysis suggested that there was a 51 % improvement in storage modulus compared to that of PLA alone, when PMDA (0.2 wt% of PMDA) was incorporated into the PLA/TTCP-AEAPS composite (5 wt% of TTCP). Using this new bioresorbable PLA composite incorporated with a more basic filler for biomedical application, the inflammation and allergic effect resulted from the degraded acidic product are expected to be reduced.

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*Corresponding author: Tel/Fax: +1-202-806-4791 (T.X. Wang), +86-10-6256-1945 (M.S. Yang). twang@howard.edu (T.X. Wang), yms@iccas.ac.cn (M.S. Yang).

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Keywords

polylactide; tetracalcium phosphate; mechanical properties; composite

1. Introduction

While metallic implants such as stainless steel and titanium alloy (e.g. Ti-25Nb-25Zr) are still the dominant products currently for bone fixation and repair [1], bioresorbable materials that could be resorbed after bone healing [2] has become more desirable due to several advantages. These include no additional removal operations after healing of the tissue; no or less stress-shielding effects than that from metallic implants; no long-term risks from permanent implant inside human body; and no interferences with diagnostic instruments such as MRI and X-ray imaging [1, 3].

As the representative bioresorbable materials already approved by the FDA, polylactide (PLA) and its copolymer, poly(lactic-co-glycolic acid), have been widely used in orthopaedic applications, such as bioresorbable bone plates and screws for internal fixation of bone fractures, fillers for bony defects and scaffolds for bone repair [4–6]. However, polymers alone usually lead to adverse clinical effects, such as the inflammatory or allergic reactions caused by the degraded acidic monomers [7].

Incorporation of biocompatible fillers into PLA matrix may provide an alternative to reduce or eliminate the inflammatory or allergic reactions of PLA. Because of their excellent tissue response and osteoconductivity [8, 9], calcium phosphate (CaP) compounds such as hydroxyapatite (HA) [10, 11] and tricalcium phosphate (TCP) [2, 10, 12, 13] have been extensively studied as fillers to be incorporated into PLA. Although HA is the mostly studied filler for PLA/CaP composites, its low solubility in physiological fluids (i.e. pH 7.2) may limit its capability to sufficiently neutralize the acidic product degraded from PLA and may significantly prolong the resorbable time of the composite materials. On the other hand, due to lack of sufficiently basic property, other fillers such as dicalcium phosphate (DCP) may not be suitable for the purpose of neutralizing the PLA degradation products *in situ*. In comparison to other CaP fillers, tetracalcium phosphate (TTCP) has a higher solubility than HA and greater basic property than any other CaP fillers [14–16]. Hydration of TTCP is expected to form calcium hydroxide [14], which can effectively compensate the released acidic monomers from PLA, thus improving tissue compatibility [8, 16–20]. Additionally, TTCP was also proved to be biocompatible and possessed osteoconductive properties [18]. Therefore, incorporating TTCP into PLA is expected to generate a new bioresorbable PLA/CaP composite which can effectively reduce the inflammation and/or allergic effects, maintain a relatively quick degradation time range (e.g. one year) and have excellent tissue compatibility [18].

In addition to the inflammation and allergic problems, another concern of the bioresorbable PLA/CaP composites is their weak mechanical properties in comparison to natural cortical bones [21]. Conventionally, PLA/CaP composites were usually fabricated by direct blending of PLA and non-modified CaP fillers [22, 23]. Due to the hydrophobic nature of PLA matrix and the hydrophilic nature of the CaP filler, direct blending of non-modified CaP with PLA

usually leads to weak interfacial adhesion, thus poor mechanical properties of the composites [24–26]. A number of strategies have been developed in the past decades to increase the interfacial strength between polymer matrix and fillers [10, 12, 24, 27–30]. As a typical example, silane coupling agents (e.g. RSiX_3) have been widely employed to improve the interfacial property [31, 32]. The X group (i.e. ethoxy or methoxy groups) within RSiX_3 [32] can react with the hydroxyl groups on the surface of inorganic nanoparticles to form covalent bonds, while the alkyl chain R can increase hydrophobicity of fillers to enhance the interactions between the PLA matrix and the fillers [33, 34]. Due to the relatively weak interaction between alkyl chain and PLA matrix in comparison to covalent bonding, the use of bifunctional organosilanes to improve the interfacial adhesion has attracted increasing attention in the past decades [12, 35–37]. The R within the bifunctional silane coupling agents can be a wide range of functional groups (e.g. amino, hydroxyl, carboxylate, mercapto, etc), which can facilitate the post-coupling reactions with the end groups of PLA, thus the interfacial adhesion can be improved [38].

In this work, an amino functionalized silane coupling agent, N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEAPS) was used to modify the surface of TTCP. While the silane moiety within AEAPS can directly react with the hydroxyl group on the surface of TTCP through silanization, the amino group of AEAPS may further react towards the terminal groups of PLA (e.g. carboxylic) [12]. In order to further improve the interfacial property, pyromellitic dianhydride (PMDA) was incorporated into the matrix. We hypothesize that PMDA can enhance the formation of covalent bonds between PLA and AEAPS modified TTCP because PMDA can react with both the amino group of AEAPS and the end group of PLA. Therefore, such covalent bonding may enhance the interfacial adhesion between PLA and TTCP, thus improving the mechanical properties [39–44].

2. Experimental

2.1. Materials

PLA (molar mass $M_w = 500,000$ g/mol) purchased from Purac Biochem (Netherland) was used to prepare the PLA/TTCP composite. TTCP represented by the formula of $\text{Ca}_4(\text{PO}_4)_2\text{O}$ was synthesized according to our method in the previous publications [45–47]. The TTCP particles were dried in the oven overnight at 110°C prior to use. Other reagents, including AEAPS (reagent grade 97 %), PMDA (reagent grade 97 %), toluene, dichloromethane, and ethanol were purchased from Sigma-Aldrich and used as received.

2.2. Preparation of functionalized TTCP

2.2.1. Surface protonation of TTCP—50 g of TTCP was dispersed in 500 mL of 1% phosphoric acid in anhydrous ethanol and the mixture was stirred at room temperature for 1 h. The mixture was washed with anhydrous ethanol according to the method in the literature [48]. The protonated TTCP particles were dried in the oven overnight at 110°C .

2.2.2. Grafting of AEAPS on the surface of TTCP—The silanization reaction was performed by refluxing a dispersion of 50 g protonated TTCP and 5 g AEAPS in 300 mL anhydrous toluene with continuous stirring under argon atmosphere at 110°C for 24 h [49].

The silanized TTCP particles (TTCP-AEAPS) were filtered and washed 3 times with anhydrous ethanol (100 mL each time) to completely remove unreacted AEAPS. TTCP-AEAPS particles were dried in the oven overnight at 110°C.

2.3. Preparation of PLA/TTCP composites

The PLA/TTCP composites were prepared by melt compounding using a Haake PolyLab OS RheoDrive 7 workstation (Germany) at 230°C with a screw speed of 50 rpm. Prior to the compounding, PLA/TTCP blends were pre-treated in the mixer for 3 min followed by adding PMDA (0.2 wt%) and mixing for another 4 min. The samples were then injected into an injection-molding machine (Haake minijet II, Thermo Fisher Scientific, Co. Ltd, Germany) at 230 °C to obtain the PLA/TTCP composites. The injection and holding time were set as 15 s and 30 s, respectively. The injection pressure and holding pressure were, respectively, 85 MPa and 15 MPa, with the mold temperature of 85°C. The obtained samples were used for measuring the mechanical properties.

2.4. Characterization

FTIR spectra were recorded using a Thermo Nicolet 6700 FTIR spectrum analyzer in the wavenumber range of (650 to 4000) cm^{-1} using a 4 cm^{-1} resolution and an average of 16 scans for each sample. The amount of surface grafted compound was characterized using thermogravimetric analysis (TGA) (Perkin–Elmer, Pyris 1) from 100°C to 750°C at a heating rate of 20°C/min with nitrogen flow of 80 mL/min. A sample with a mass of 3.0 mg $\pm$ 0.1 mg was used for each measurement. The amount of silane on the surface of TTCP was calculated based on the weight loss percentage from the TGA curves. A Field Emission Scanning Electron Microscope (FE-SEM) (JSM-6700F, JEOL) was employed to observe the morphology of the fracture surface of PLA/TTCP. Prior to the SEM examination, samples were submerged in liquid nitrogen for 30 minutes and broken to expose the internal structure for SEM studies. The tensile property was characterized at room temperature according to ISO 527 on an Instron 3365 universal test machine (Instron Corporation, USA). The cross-head speed of the apparatus was 5 mm/min. The bending property was measured at room temperature according to ISO 178 on an Instron 3365 machine at a bending speed of 1 mm/min. The mechanical data were obtained by averaging of three specimens. Dynamic mechanical analysis (DMA Q800, TA Instruments) was performed with a single-cantilever clamp on sample bar measuring 35×4×2 mm³. A temperature ramp experiment was conducted with an amplitude of 15 μm from –50°C to 150 °C at a heating rate of 3 °C/min with a constant frequency of 1 Hz.

3. Results and discussion

3.1. Grafting of AEAPS on the surface of TTCP

As shown in Scheme 1, preparation of PLA-TTCP composites was achieved by two steps. The surface of TTCP particle was first functionalized with AEAPS. In the second step, the amino groups on AEAPS were covalently linked with PLA. AEAPS modified TTCPs were prepared with both protonated and non-protonated TTCPs. Due to a lack of sufficient number of the reactive hydroxyl groups on the surface of TTCP, TTCP was pre-protonated prior to AEPAS silanization. The effect of pre-protonation of TTCP on the grafting

efficiency of AEAPS was evaluated by thermogravimetric analysis. Fig. 1 shows that the protonated TTCP had good thermal stability and no significant mass loss ($\sim 0.4\%$) was observed until 750°C . After AEAPS was grafted onto the protonated-TTCPs, a significant decrease of thermal stability of the protonated TTCP-AEAPS was observed (5 wt% mass loss at 750°C). This significant mass loss could be attributed to the decomposition of the AEAPS grafted on the surface of TTCP. In contrast, no obvious differences in mass loss were observed from the non-protonated TTCP with and without AEAPS modification. This confirms that AEAPS was difficult to be grafted on the non-protonated TTCP. The reason can be that protonation of TTCP could generate sufficient amount of hydroxyl groups, which could facilitate the AEAPS silanization of TTCP. The importance of pre-protonating TTCP prior to silanization observed in this study is consistent with the previous study [48].

Grafting of AEAPS from the surface of TTCP was additionally examined by FTIR (Fig. 2). The broad peak at $3700\sim 3200\text{ cm}^{-1}$ observed in both TTCP and TTCP-AEAPS can be attributed to the stretching of hydroxyl and amino groups [50]. Compared to the broad band of TTCP below 1700 cm^{-1} , TTCP-AEAPS shows more resolved absorption. The characteristic absorption peaks at 1650, 1455, and 1417 cm^{-1} corresponding to the absorption peaks from AEAPS-TTCP composites were clearly observed. Particularly, the peak at 964 cm^{-1} observed in TTCP-AEAPS only confirms the formation of P-O-Si covalent bond [12]. The peak at 877 cm^{-1} could be assigned to the bending vibration of N-H, indicating the success modification of AEAPS on TTCP.

In addition to FTIR examination, dispersion of TTCP and TTCP-AEAPS was compared to understand the effect of AEAPS modification. The dispersion was investigated by suspending 0.5 g of either TTCP or TTCP-AEAPS in 4 mL dichloromethane under stirring for 10 minutes. Fig. 3 shows that, after the stirring was stopped, TTCP precipitated and settled immediately, while the TTCP-AEAPS suspension was stable even after 20 minutes. This confirms that silanization of TTCP with AEAPS could reduce the agglomeration of TTCP in organic solvent, which is one key to improve the dispersion of TTCP within the PLA matrix, thus improving the mechanical properties of PLA/TTCP composites.

3.2. Mechanical properties of PLA-TTCP composites

In order to understand the effects of the interfacial improvement and weight ratio of TTCP within the composites on the mechanical property enhancements, mechanical properties including tensile strength and bending strength of PLA-TTCP composites with varied TTCP contents (0, 5, 10 and 20 wt%) were studied. The composites were prepared from three different compositions, e.g. non-modified TTCP (PLA/TTCP), AEAPS modified TTCP (PLA/TTCP-AEAPS), and AEAPS modified TTCP with the presence of PMDA as the cross-linker (PLA/PMDA/TTCP-AEAPS).

As shown in Fig. 4, AEAPS modification significantly improved the tensile strength of the PLA-TTCP composites. In comparison to PLA alone, all tested PLA-TTCP composites showed a decreased tensile strength with the increase of TTCP content, which is similar to the conventional PLA/HA composites [51]. However, although the strength dropped linearly for all PLA/TTCP composites, the composites prepared with the AEAPS modified TTCP showed less decrease in tensile strength than that of non-modified TTCP.

Particularly, no significant decreases in tensile strength of both PLA/TTCP-AEAPS and PLA/PMDA/TTCP-AEAPS were observed when the loading percent of TTCP increased from 10% to 20 wt%. Although the tensile strength of the composites prepared from AEAPS modified TTCP at 20 wt% was lower than that of PLA alone, it was significant greater than that from non-modified TTCP at the same TTCP ratio. At 20 wt% of TTCP, AEAPS modification improved the tensile strength by 32% to 68.4 MPa from that of non-modified TTCP (51 MPa). The significant improvement of the tensile strength by AEAPS modification at a high TTCP loading ratio was significant because a high loading ratio of calcium phosphate fillers is normally required in order to fulfill the neutralizing capability and improve the biocompatibility [52].

This indicates that modification of TTCP with AEAPS has the effect to improve the tensile strength, either by improving the dispersion or enhancing the interfacial adhesion through covalent bonds. It is well known that the agglomeration of the inorganic fillers is one key problem resulting in material defects, thus weaker mechanical strengths, especially at a high loading [10, 53]. Reduction of agglomeration by modifying TTCP with AEAPS could contribute to the dispersion of TTCP within the PLA matrix, thus improve the tensile strength.

However, although we hypothesized that addition of PMDA may further enhance the formation of covalent bonds between PLA and TTCP and thus improve the mechanical strengths of the composites, no significance effect from PMDA, particularly when TTCP is 10 wt% or 20 wt%, was observed. When TTCP is 5 wt%, it seems that PMDA incorporation showed an additional enhancement in tensile strength, but it was not confirmed from the composites with 10% or 20% TTCP. At 5 wt% of TTCP, the tensile strength of composite from AEAPS modified TTCP were improved to 78 MPa (in the presence of PMDA) or 73 MPa (in the absence of PMDA), respectively, from 71 MPa of composites prepared from non-modified TTCP. When TTCP is 20%, AEAPS modification improved the tensile strength to 68 MPa from 51 MPa of the composite, but the tensile strength either with or without PMDA are almost the same. While it was hypothesized that PMDA can enhance covalent bond formation between AEAPS and PLA, the obtained results implied that there was no obvious effect from PMDA to the mechanical enhancement.

While better interfacial adhesion between filler and polymer matrix is good for load transfer [48, 54], there is no experimental evidence to prove the covalent bonding between PLA and AEAPS, with or without PMDA. An additional experiment on FTIR (data not shown) has been performed, but covalent bond formation between PLA and PMDA or AEAPS was not observed. This implies that either no covalent bond formation or the absorption of the C–N from the formed amide might be too weak to be observed in comparison to other stronger peaks such as $-(C=O)-O-$ from PLA. At least, AEAPS modification indeed increased the mechanical strength. Such enhancement could be attributed to the dispersion enhancement of TTCP in the present study. The improvement of the distribution of AEAPS modified TTCP into PLA matrix could be also due to the possible hydrogen bonds between amino group from AEAPS and the oxygen from PLA. The less effect from PMDA, particularly at a higher TTCP ratio, might be due to the agglomeration, which compromised the PMDA enhancement.

In comparison to the tensile strength, the tensile modulus of all PLA-TTCP composites increased with incorporation of TTCP particles. The composite prepared from TTCP-AEAPS had greater modulus than that from the non-modified TTCP. This might be attributed to the better distribution of TTCP within PLA after silanization as well as the improved interfacial properties, especially at higher loading. After incorporating TTCP-AEAPS into the matrix (20 wt%), the tensile modulus increased to 2000 MPa from 1550 MPa of the pure PLA.

However, when PMDA was incorporated into the matrix, the modulus has no obvious increase in comparison to that without PMDA. Although PMDA was expected to enhance the interfacial adhesion by reacting with the terminal hydroxyl groups of PLA and the amino group of the TTCP surface, there is no obvious effect to modulus enhancement. It might be due to that the reaction between anhydride and amino group occurred during the compounding process might be too limited to be observed. This is in agreement with FTIR spectra (data not shown), in which no obvious $-(C=O)-N-$ absorption was observed [41].

The bending test showed a similar behavior as that from the tensile test. The bending strength decreased with increase of TTCP ratio, while the modulus decreased. Unlike the tensile strength, there was no obvious effect in the bending strength and modulus from AEPAS modification and PMDA cross-linking with the same TTCP ratio. Because TTCP tended to agglomerate at high TTCP loading ratio, the bending strength dropped dramatically even for the PLA/TTCP-AEAPS composites with increase of TTCP ratio. Increasing TTCP fraction increased the agglomeration and more cracks could form and develop, thus decreasing the bending strength of the composites. The similarity of the bending strength between the composites from the AEAPS modified and non-modified TTCP with the same TTCP ratio indicates that the interfacial strength between the particles and matrix was not sufficiently strong [55]. Although it has been reported that the surface modification could have the potential to improve the interfacial adhesion [12], our results from bending test suggested these interactions were weak or negligible.

3.3. Dynamic mechanical property of PLA/TTCP composites

Fig. 6 shows the dynamic storage modulus of PLA and PLA/TTCP composites (5 wt%) over a temperature range of -50 to 150°C . It was found that the storage modulus increased with incorporation of filler over the entire temperature range. At -50°C , the storage modulus for PLA was 3.21×10^9 Pa. The storage modulus decreased with the increasing temperature and dropped dramatically around the glass-transition temperature ($T_g = 58.9^{\circ}\text{C}$). This was attributed to lack of sufficient thermal energy to overcome the potential barrier for transitional and rotational motions of segments of the polymer molecules in the glassy region. In contrast, when the temperature was above T_g , the thermal energy increased, so it was high enough to overcome the potential energy barriers for the segmental motions.

For the composite with 5 wt% of TTCP, notable enhancement of the storage modulus (32 % increase) was observed in the lower temperature range, indicating that addition of TTCP had remarkable influence on the elastic properties of the PLA matrix. By incorporating TTCP-AEAPS (5 wt%) into the matrix, the storage modulus of the composite was 4.62×10^9 Pa, which was 44 % greater than that of PLA alone.

The above results indicated that AEAPS modification was beneficial for the compatibility between PLA and TTCP (Fig. 7). When 0.2 wt% PMDA was incorporated into the composites, the storage modulus was increased to 4.88×10^9 Pa (51 % increase). While not supported by direct evidence, the potential reaction between anhydride from PMDA and the amino group from AEAPS-TTCP [41] could lead to an enhanced interfacial property (Fig. 7B). In addition, the anhydride might also react with the terminal hydroxyl group of PLA [40, 44], so the interface between PLA and TTCP was improved. These two factors made contribution to the additional increase of the storage modulus. However, the degree of reaction between amino group and anhydride might be too low to be observed. At least, the possible hydrogen bonds formed between PLA and AEAPS could further enhance the compatibility between PLA and TTCP. T_g increased from 63.2°C for PLA/TTCP-AEAPS (5%) to 65.5°C when PMDA was incorporated into the composite (Fig. 6B), suggesting that a better interface was generated.

4. Conclusion

A new bioresorbable composite was successfully prepared by incorporating a basic calcium phosphate filler, i.e. TTCP into PLA matrix. In comparison to the PLA/TTCP composite from the non-modified TTCP, the mechanical property of the PLA/TTCP composite was improved by using an amino functionalized silane coupling agent combining with a PMDA cross-linker. While the silane can bind with TTCP through silanization reaction, the amino group can form covalent bonds with PLA through PMDA cross-linker, and thus the interfacial property between PLA and TTCP was enhanced. FTIR confirmed that new chemical bond was formed between AEAPS and TTCP. TGA further confirmed 5 wt% AEAPS has been grafted onto the surface of TTCP. The tensile strength increased from 51.5 MPa of PLA/TTCP to 68.4 MPa of PLA/TTCP-AEAPS composite (20 wt% TTCP). From dynamic mechanical analysis, a 44% increase in storage modulus was found when TTCP-AEAPS was incorporated into PLA matrix. By adding 0.2 wt% of PMDA into the composite, an additional 7 % increase in storage modulus was observed. In addition to the mechanical improvement, the basic TTCP filler could have greater capacity to neutralize the acidic products degraded from PLA and enhance the tissue compatibility, which is being under investigation. Eventually, this new bioresorbable PLA/CaP composite with improved mechanical properties and more basic TTCP filler could have the potential to be applied to load-bearing location for bone fixation and repair with additional benefit to reduce inflammatory or allergic effect caused from the acidic products degraded from PLA.

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Highlights

- A new bioresorbable composite was prepared from PLA and a more basic TTCP filler.
- TTCP filler may reduce inflammation by neutralizing the acid degraded from PLA.
- AEAPS and PMDA were used to improve the interfacial and mechanical strength.

Figure 1. TGA curves of TTCP particles (protonated and non-protonated) as well as AEAPS modified TTCP particles from the above protonated and non-protonated TTCP particles.

Figure 2.
FTIR spectra for TTCP particles and AEAPS modified TTCP particles (TTCP-AEAPS).

Figure 3.
Photographs of TTCP particles and AEAPS modified TTCP particles (TTCP-AEAPS) dispersed in dichloromethane for different time.

Figure 4.

Tensile properties of PLA/TTCP composites (a) from non-modified TTCP (PLA-TTCP); (b) from AEAPS modified TTCP without PMDA (PLA/TTCP-AEAPS); and (c) from AEAPS modified TTCP with the presence of PMDA (PLA/PMDA/TTCP-AEAPS). (Left) tensile strength; (Right) tensile modulus.

Figure 5. Bending properties of PLA/TTCP composites prepared (a) from non-modified TTCP (PLA-TTTP); (b) from AEAPS modified TTCP without PMDA (PLA/TTCP-AEAPS); and (c) from AEAPS modified TTCP with the presence of PMDA (PLA/PMDA/TTCP-AEAPS). (Left) bending strength; (Right) bending

Figure 6.

DMA curves of PLA/TTCP composites: (Left) the storage modulus; (Right) the loss modulus.

Figure 7.
SEM images of the composites: (A) PLA/TTCP-AEAPS (5 wt%); (B) PLA/PMDA/TTCP-AEAPS (5 wt%).

Scheme 1.
Reaction scheme of PLA-PDMS-TTCP-AEAPS