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Synthesis and characterization of MMA–NaAlg/hydroxyapatite composite and the interface analyse with molecular dynamics

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ABSTRACT

A novel composite of α-methyl methacrylate (MMA) grafted sodium alginate (NaAlg) and hydroxyapatite (HA) was prepared in this study. The compositions and chemical groups of materials were investigated by infrared spectra (IR), X-ray diffraction (XRD) and nuclear magnetic resonance (NMR). The results showed that MMA has been successfully grafted with the hydroxyl group of sodium alginate. Moreover many chemical bonds existed in the composite, including the "egg-box" structure and hydrogen bonding. Meanwhile, the chemical bondings between MMA and sodium alginate partly replaced the intermolecular hydrogen bonding or the intramolecular hydrogen bonding in sodium alginate. The composite had better water contact angle than sodium alginate, indicating the strong hydrophilic character of pure sodium alginate was improved. The molecular dynamics (MD) method was used to simulate and evaluate the interaction energies based on the theoretics, which suggested that the copolymer whose every monomer grafted with one MMA had a more stable structure.

1. Introduction

Sodium alginate (NaAlg, $(C_6H_7O_6Na)_n$) is a linear anionic polysaccharide occurring naturally which belongs to carbohydrate group of polymers, found in brown algae. It is mainly composed of β-D-1, 4-mannuronic acid (M unit) and α-L-1, 4-guluronic acid (G unit) (Salomonsen, Jensen, Stenbak, & EngelsenSoren, 2008; Sriamornsak, Nunthanid, & Manee, 2007; Veerapur, Gudasi, & Aminabhavi, 2008). The residues may vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. The homopolymeric regions of M and G blocks are interspersed with regions of alternating structure (MG blocks) (Anisha & Prema, 2008; De & Robinson, 2003; Almeida & Almeida, 2004; Lin, Cui, Li, & Du, 2006). The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. One of the most important and useful properties of alginates is the ability to form gel in the presence of some multivalent metal ions such as calcium (Salvati et al., 2008; Tong, Wu, & Zhu, 2002).

As a natural biopolymer, alginate has been found increasing biotechnological and biomedical applications in view of its several advantages, such as good biocompatibility, biodegradability, non-toxicity, non-immunogenicity, chelating ability, and the possibility of chemical modification. However, sodium alginate has limited application in clinic because itself and its gel have lower mechanical strength and strong hydrophilic character. To improve the mechanical strength of sodium alginate, current works focused mainly on the addition of different cross-linker such as different metal ions, glutaraldehyde, poly-L-lysine, ethylene acid hydrazine (Gomez Cesar, Chambat, & Heyraud, 2006; Gomez, Rinaudo, & Villar, 2007; Kuzuya, Izumi, & Sasai, 2004; Zhang, Gong, & Lu, 2004). However, the mechanical strength of sodium alginate did not get great improvement with these methods (Mollah, Khan Mubarak, Hoque, & Aziz, 2008).

Grafting as a technique for modifying chemical and physical properties of natural polymers has attracted much interest (Laurienzo, Malinconico, Motta, & Vicinanza, 2005; Yang, Zhang, & Wen, 2007). But in the early literatures, MMA was rarely used to graft with sodium alginate although it has good mechanical property and biological properties. So in this study, MMA was grafted onto sodium alginate in the presence of initiator, then hydroxyapatite was introduced into the reaction system for its good bioactivity and biocompatibility to prepare the composite of MMA–NaAlg copolymer and HA.

The interface between polymer and HA plays a vital role in investigating the miscibility, adhesion characteristics and biological degradability of the composite (Nagasawa, Mitomo, & Yoshii, 2000). Nevertheless, traditional experimental methods provide few details about the surface interaction and surface adsorption phenomena of the interface. The molecular dynamics (MD) meth-

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od, which is widely used in material design and evaluation, provides a theoretical and numerical framework for many particle problems (Ma, Zhao, & Ji, 2008; Wu & Xu, 2007; Heuchel, Fritsch, & Budd Peter, 2008). Especially, MD could be an effective method to evaluate the interaction energy and surface energy of the interface between polymer and inorganic material in composite (Prathab, Subramanian, & Aminabhavi, 2007a, 2007b; Yuan Cadmus, Sluis, & Zhang, 2007). Therefore, we simulated the interfaces between polymers (NaAlg, MMA, MMA–NaAlg) and HA, and investigated their interaction energies, compatibility behavior and adhesion characteristics from the details of MD simulation.

2. Materials and methods

2.1. Materials

Hydroxyapatite (HA) slurry was prepared hydrothermally from Ca $(NO_3)_2$ and Na_3PO_4 according to a method used in our previous study (Mo, Li, Lv, Li, & Yang, 2006). Sodium alginate (M_w = 122,594) was purchased from Shanghai Chemistry Reagent Factory (China). Formamide, α-methyl methacrylate (MMA), dimethyl formamide, *p*-toluenesulfonic acid, vinyl acetate and potassium peroxydisulfate (KPS) of Analytical Reagent (AR) grade were supplied by Chengdu Kelong Chemistry Reagent Company (China).

2.2. Preparation of composite material

Sodium alginate solution (5% w/v, 100 ml H_2O) was treated with a mixture of *p*-toluenesulfonic acid (1.5 g), dimethyl formamide (27 ml) and formamide (30 ml). The reaction was taken at 333 K with stirring for 1 h. Then, 25 ml MMA, 20 ml vinyl acetate and 0.2 g KPS as the initiator were added into the solution with constant stirring at 358 K. After stirring for 2 h, 20 ml HA slurry (20% w/v) was added into the solution at 358 K for 3 h with stirring. Then the reaction solution was washed with ethanol for 5 times and dried at 353 K for 48 h.

2.3. Fourier transform infrared spectroscopy (FTIR) studies

To evaluate the changes of functional groups in every process, samples were collected in each process and scanned using Nicolet-170SX FTIR spectrophotometer in the wavelength range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1} at ambient temperature.

2.4. X-ray diffraction analysis

X-ray diffraction analysis was carried out by means of a Fangyuan DX-2600 powder diffractometer. Cu Kα radiation (λα = 1.54184) was used. The 2θ range was from 10° to 80° and the data were collected with an acquisition time of 5.0 s at a 0.03° step size.

2.5. NMR analysis

Alginate and MMA–NaAlg copolymer were determined by ^1H NMR spectrometry, using polymer samples dissolved in D_2O (99.9%, Cambridge Isotope Laboratories, Inc.) at a concentration of 4 mg/mL. ^1H NMR experiments were performed using Bruker AV II-400 MHz spectrometer at 300 K with 16 scans number for proton. The acquisition time was 4s.

2.6. Macroscopic contact angle measurement

Macroscopic water contact angles on the surfaces of pure sodium alginate membrane and MMA–NaAlg/HA composite membrane were evaluated by the drop shape analysis system JC2000C1 + goniometer (Powereach, China). Water drops were automatically formed at the needle end and deposited on the surface. Once deposited, they were allowed to settle for 10s to ensure that measured contact angle referred to equilibrium condition.

2.7. Estimation of interaction energies

To evaluate the interaction energies between sodium alginate and MMA as well as the interaction energies between polymers and HA, MD (molecular dynamics) simulation and calculation were performed by software Materials Studio 4.0. The COMPASS (condensed-phase optimized molecular potentials for atomistic simulation studies) force-field was used (Sun, 1998), which is one of the first ab initio force-field approaches that has been parameterized and validated using the condensed-phase properties.

The unit cell structure of HA was built using the surface builder module of MS modeling. The cleave plane (h k l) was generated with the non-bonded cut-off distance 9.5 Å. After completing the energy minimization, surface structure was converted into a non-periodic superstructure. The simulation boxed to calculate the surface energy was built, and the monomer of NaAlg, MMA and the oligomer of MMA–NaAlg copolymer were to 30 Å such that the polymers were at an equidistance from the HA surface and assembled into the simulation boxes respectively. Then the *c*-dimension of the box was extended.

The interaction energies of NaAlg/HA, MMA/HA and MMA–NaAlg/HA can be calculated according to the following equation:

$$E_{\text{interaction}} = E_{\text{total}} - (E_{\text{surface}} + E_{\text{polymer}}) \quad (1)$$

At first, the energy (E_{total}) for the simulation box containing HA and polymer with the surface atoms was calculated. Then, the energy of polymer (E_{polymer}) was calculated without any contribution from the surface. Finally, surface atoms were kept constant and polymer was removed to calculate the surface energy (E_{surface}). The interaction energies of polymers/HA were then computed.

3. Results and discussion

3.1. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of sodium alginate, sodium alginate treated with the mixture of *p*-toluenesulfonic acid, dimethyl formamide and formamide, HA and the final MMA–NaAlg/HA composite are presented in Fig. 1. It is can be seen from Fig. 1a that the obvious peaks at 1615 and 1417 cm^{-1} are attributed to the —COO^- asymmetric stretching and symmetric stretching of carboxyl groups in sodium alginate. The small peaks at 619 and 1310 cm^{-1} belong to the O—CO in-plane deformation vibration of carboxyl group and C—H deformation vibration in sodium alginate, and the tiny peak at 891 cm^{-1} is the characteristic peak of the O—Na vibration of sodium alginate. The broad peak at 3427 cm^{-1} is due to H_2O vibration and the peak at 2939 cm^{-1} corresponds to the —OH stretching vibration (Sanli, Nuran, & Nuran, 2007).

Fig. 1b shows the spectrum of sodium alginate after treated with the mixture of *p*-toluenesulfonic acid, dimethyl formamide and formamide. Compared with pure sodium alginate, a tiny peak appears at 2845 cm^{-1} which belongs to the O-stretching vibration of modified hydroxyl group in sodium alginate. Moreover, a sharp peak is present at 1385 cm^{-1} because Na^+ ions of —COONa in sodium alginate were partly replaced by H^+ ions in the process of treatment.

The FTIR spectrum of the final MMA–NaAlg/HA composite is shown in Fig. 1d. The characteristic peaks of PO_4^{3-} in HA at about 1090 and 598 cm^{-1} exist in Fig. 1d with small shift com-

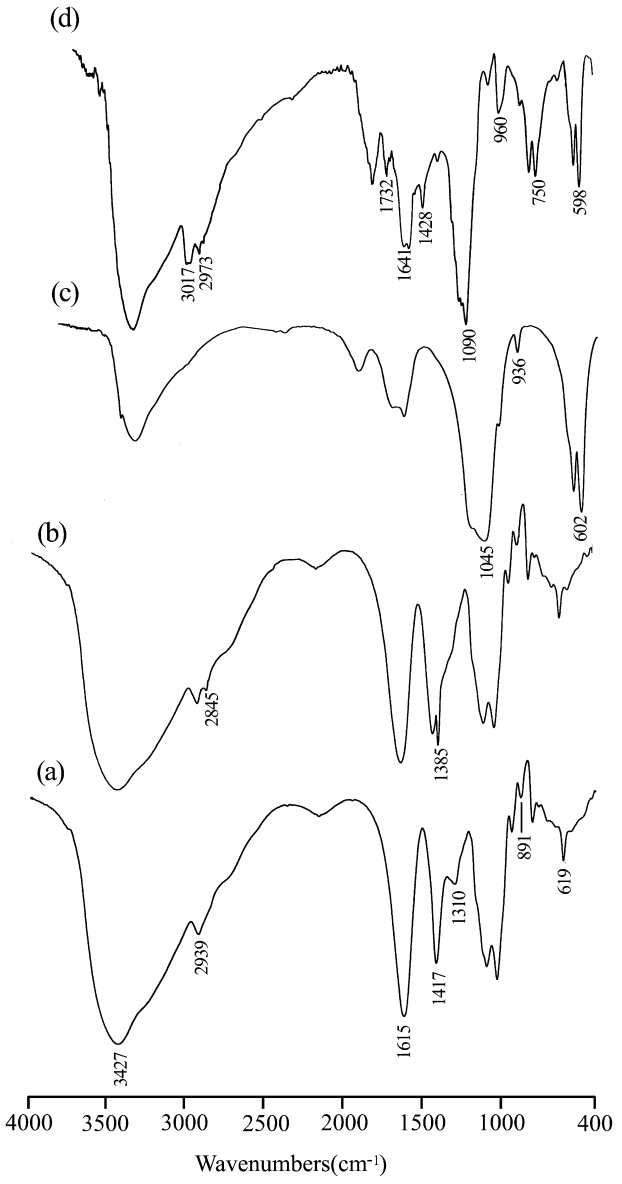


Fig. 1. IR spectrums of pure sodium alginate (a), the sodium alginate treated with the mixture of *p*-toluenesulfonic acid, dimethyl formamide and formamide (b), HA (c) and the final composite (d).

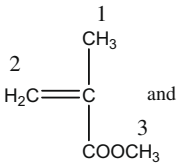
paring the spectrum of HA in Fig. 1c. The C=C—H stretching vibration peak of MMA appears at 3017 cm^{-1}, the —C=O stretching vibration peak of —COO group in MMA at 1732 cm^{-1} and the —CH_2— absorption peak of MMA at 750 cm^{-1}. These peaks indicate that MMA has been successfully grafted onto alginate. Scheme 1 illustrates this process: many radicals were generated in sodium alginate solution after treated with the mixture of *p*-toluenesulfonic acid, dimethyl formamide and formamide. When MMA and initiator were introduced into the solution, it was easy to connect the radicals with chemical bond (Qiu, 2008). Also, the aggregate reaction from MMA to PMMA carried out at the grafting process. Furthermore, the main peaks of —COO^- group at 1615 and 1417 cm^{-1} shift to lower frequency because of the cross-linking formation between the G units of sodium alginate and Ca^{2+} in HA, which called "egg-box" structure. As shown in Fig. 2, each calcium ion takes part in nine coordination link with an oxygen atom, resulting in three-dimensional network of calcium alginate (Ching, Liew, Heng, & Chan, 2008; Solak & Sanli, 2008). Moreover, hydrogen bonding also exists in the composite because the stretching vibration peak of hydroxyl group shifts from high frequency to lower frequency.

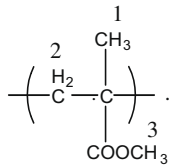
3.2. XRD analysis

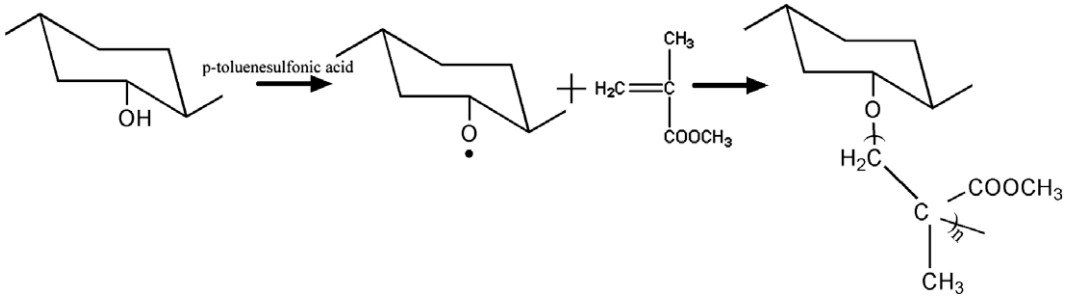
The XRD patterns of sodium alginate, HA and the MMA–NaAlg/HA composite are shown in Fig. 3. As presented in Fig. 3a, pure sodium alginate has weak characteristic peaks at about 10° and 20°. But in the pattern of MMA–NaAlg/HA composite in Fig. 3c, the characteristic peak at 10° disappears and the peak at 20° is weaker than before. This should be due to the partial replacement of the intermolecular hydrogen bonding or the intramolecular hydrogen bonding in sodium alginate by the chemical bonding between MMA and sodium alginate. It destroys the organization of the chains in alginate and decreases the orderliness of structure array and the crystallinity. Compared with the pattern of HA in Fig. 3b, the main characteristic peaks of HA are present in the MMA–NaAlg/HA composite but weaker than before, because most of HA particles are wrapped by the copolymer of sodium alginate and MMA.

3.3. NMR analysis

The ^1H NMR spectrum of sodium alginate is shown in Fig. 4a. Because HA is hard to dissolve in aqueous solution and D_2O, MMA–NaAlg composite was prepared for NMR without adding HA slurry at the reaction process. To estimate the effect of graft, the ^1H NMR spectrum of the MMA–NaAlg is presented in Fig. 4b.

MMA has the structure of  and

the structure of PMMA is  .



Scheme 1. Graft of MMA on sodium alginate.

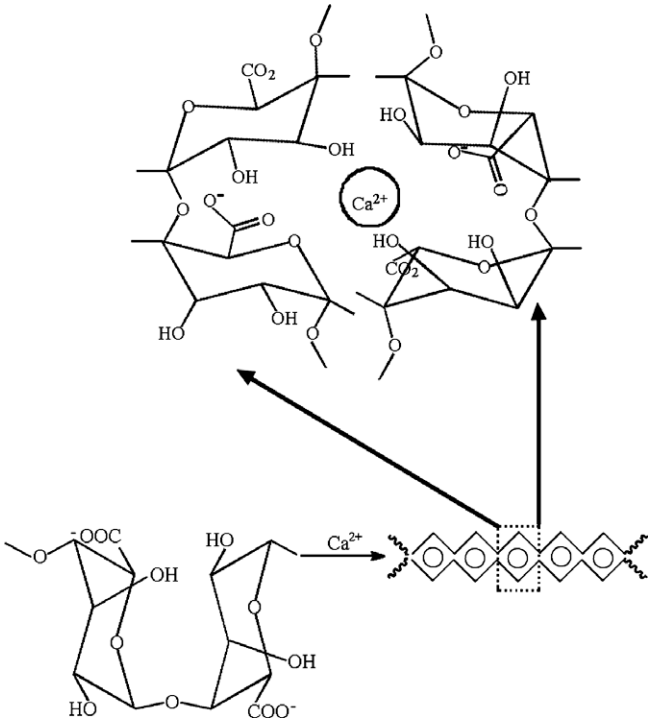


Fig. 2. The "egg-box" structure in the final composite.

In contrast with the spectrum of sodium alginate: (1) several new signals appear in the range of 1.0 to 2.0 ppm which are attributed to the protons of MMA graft. The intensive signal at 1.7 ppm results from the H (site 2) corresponding to —CH_2— group in MMA and =CH_2 group in remnant MMA. Meanwhile, the signal for H (site 1) of —CH_3 group in MMA appears at 1.4 ppm. (2) The obvious signal at 3.8–4.0 ppm is assigned to the H (site 3) of COO—CH_3 group in MMA (Wang & Ando, 1999a, 1999b).

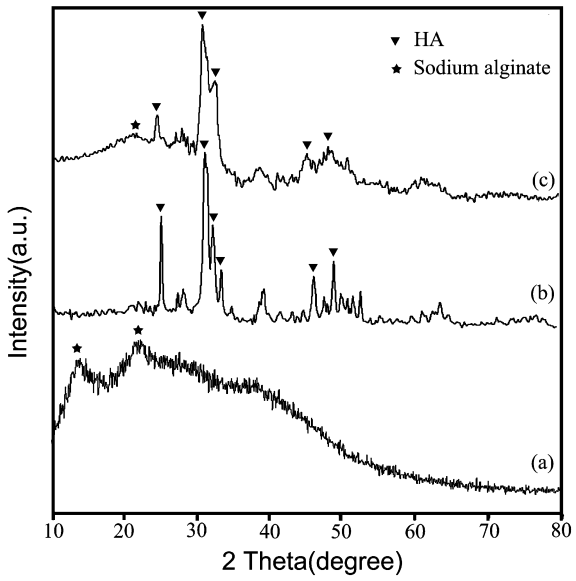


Fig. 3. XRD patterns of sodium alginate (a), HA (b) and the MMA–NaAlg/HA composite (c).

3.4. Water contact angle

The corresponding water contact angle was tested to be 59 ± 1° after water formed stable symmetrical macroscopic droplets on the surface of sodium alginate membrane. Meanwhile, the water contact angle of MMA–NaAlg copolymer was 61 ± 1°. However, the contact angle on the surface of MMA–NaAlg/HA composite membrane rised to 67 ± 1°. The result suggests that the composite increases the hydrophobic character of pure sodium alginate, i.e., the strong hydrophilic character of pure sodium alginate has been improved. It is known that the strong hydrophilic character of pure sodium alginate can limit the migration and nutrition exchange of cells, so we infer that the composite material should have better biological properties than pure sodium alginate.

3.5. Simulation and calculation of interface

In Fig. 5, it can be seen that each sodium alginate monomer comprises eight hydroxyl groups with different locations. These hydroxyl groups result in many possible constitutions and structures when MMA is grafted on NaAlg: (a) one NaAlg monomer bonds with one MMA; (b) one NaAlg monomer bonds with many MMA until all hydroxyl groups are grafted with MMA.

Block copolymers of NaAlg and MMA have been generated with the construction strategy as implemented in Materials Studio 4.0. An illustration of the typical structure of block copolymers of MMA and NaAlg is shown in Fig. 6. The sequence of block copolymer is represented as *n*-MMA–NaAlg where *n* specifys the labeled number of hydroxyl group in Fig. 5 bonding with MMA monomer. For example, the copolymer is named 1-MMA–NaAlg when the hydroxyl group labeled '1' grafts with MMA, and its structure model is presented in Fig. 6. The bond connecting NaAlg and MMA is pointed by an arrow in the figure.

To assess the preferred site of MMA bounding to NaAlg, energy calculations with the DISCOVER Module were carried out, the simulations and calculations were conducted at constant temperature (NVT) and conditions. Some of the results are shown in Table 1. It can be seen that the total energy value of pure sodium alginate is 986.44 kcal mol^{-1} which is the weakest one in all samples, indicating a more stable structure than copolymers. The energy of 1-MMA–NaAlg calculated to be 1051.60 kcal mol^{-1} is close to the energies of other copolymers whose structure has one MMA unit in each monomer. Meanwhile, the total energies of the copolymers increase with the number of MMA units grafted on one sodium alginate monomer. It is also observed that the structure has the highest energy (1793.95 kcal mol^{-1}) when all hydroxyl groups in NaAlg monomer are bonded with MMA. Total energy plays a vital role when discussing the stability of different structures. In general, the structure with lower energy has better stability and is much easy to be prepared. Therefore, if one alginate monomer grafted with only one MMA, the copolymer will have a more stable structure and is easy to be produced. In such a situation, the MMA–NaAlg copolymer has eight structures with different grafting state. But there are no obvious changes of the calculated energies among these structures.

Materials Studio 4.0 was used to simulate and calculate the interaction energies between different polymers and HA (Tables 2 and 3). In the case of MMA/HA, the interaction energy is −339,957 kcal mol^{-1}, while NaAlg/HA has greater interaction energy of −641,647 kcal mol^{-1}, indicating NaAlg has stronger linking with HA than MMA even if the "egg-box" structure between NaAlg and HA is ignored. The calculated interaction energy of MMA–NaAlg/HA is −778,320 kcal mol^{-1} which is greater than others, revealing that the copolymer of MMA–NaAlg has the strongest connection with HA.

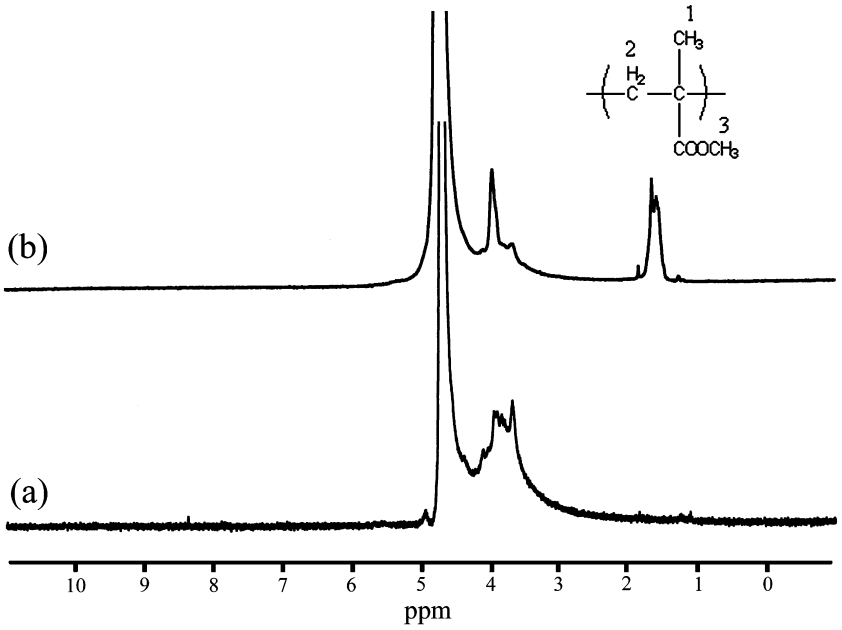


Fig. 4. ^{1}H NMR spectra of sodium alginate (a), and the composite MMA–NaAlg (b) in D2O solvent.

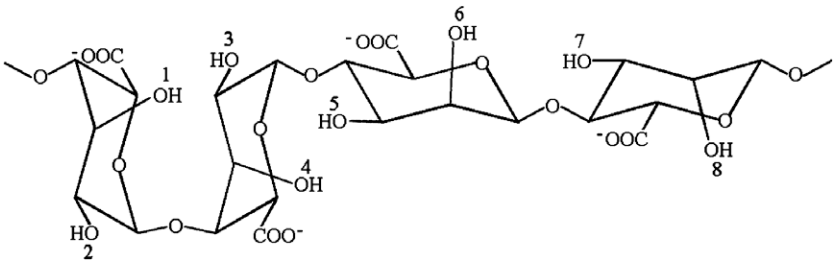


Fig. 5. The chemical structure of sodium alginate monomer and the labeled different sites of hydroxyl group.

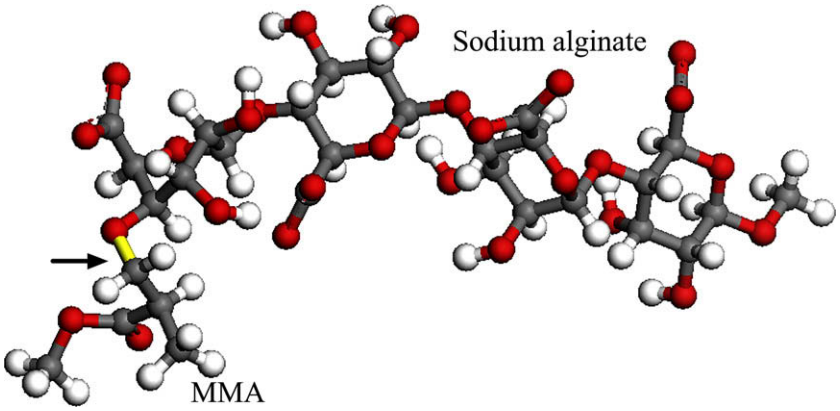


Fig. 6. The model of sodium alginate grafted with MMA simulated by Materials Studio 4.0 (colors: carbon atoms-grey, hydrogen-white and oxygen-red). The bond connecting NaAlg and MMA is pointed by an arrow.

4. Conclusions

In this study, the composite of MMA grafted sodium alginate and hydroxyapatite was prepared. The results showed that many chemical bonds existed in the composite, including the "egg-box" structure and hydrogen bonding between sodium alginate and hydroxyapatite. The chemical bondings between MMA and sodium alginate partly replaced the intermolecular hydrogen bonding or the intramolecular hydrogen bonding in sodium alginate, which destroyed the organization of the chains in alginate and decreased the orderliness of structure array and the crystallinity. The composite had better water contact angle than sodium alginate, indicating the strong hydrophilic character of pure sodium alginate was improved and the compostie should have better biological properties. The molecular dynamics method suggested that when one alginate monomer was grafted with one MMA, the copolymer

Table 1
The energies of different copolymers calculated by Materials Studio 4.0.

Copolymer	Total energy (kcal/mol)	Internal energy (kcal/mol)	Non-bond energy (kcal/mol)
Sodium alginate	986.44	563.79	422.65
1-MMA-NaAlg	1051.60	556.94	494.66
2-MMA-NaAlg	1054.90	565.01	489.89
3-MMA-NaAlg	1039.19	561.53	477.66
4-MMA-NaAlg	1042.49	565.01	477.48
5-MMA-NaAlg	1072.36	600.69	471.67
6-MMA-NaAlg	1060.75	607.40	453.35
7-MMA-NaAlg	1059.98	605.23	454.75
8-MMA-NaAlg	1067.40	601.09	466.31
1,2-MMA-NaAlg	1105.79	622.49	483.30
1,4-MMA-NaAlg	1108.56	625.31	483.25
4,6-MMA-NaAlg	1112.18	627.14	485.04
6,8-MMA-NaAlg	1109.35	623.35	486.00
1,2,6-MMA-NaAlg	1170.14	693.72	476.41
4,6,8-MMA-NaAlg	1175.62	694.16	481.46
1,3,6,8-MMA-NaAlg	1288.57	741.25	547.32
1,3,5,6,7-MMA-NaAlg	1408.12	835.82	572.30
1,2,4,5,7,8-MMA-NaAlg	1666.62	957.35	709.27
1,2,3,5,6,7,8-MMA-NaAlg	1777.09	1103.29	673.80
1,2,3,4,5,6,7,8-MMA-NaAlg	1793.95	1029.23	764.72

Table 2
The surface energies of different crystal forms for HA.

Crystal forms	Surface energy (kcal/mol)
(001)	−13233.61
(100)	−10122.75
(002)	−13234.55
(012)	−9996.35

Table 3
The interaction energies of different simulated interfaces.

Interfaces	Interaction energy (kcal/mol)
MMA/HA	−339957
NaAlg/HA	−641647
MMA-NaAlg/HA	−778320

would have a more stable structure. The MMA–NaAlg/HA composite has relatively lowest interface energy, indicating the copolymer has the strongest linking with HA than the single polymers of MMA and NaAlg.

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