Injectable thermo-responsive hydrogel composed of xanthan gum and methylcellulose double networks with shear-thinning property

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ABSTRACT

Injectable hydrogel precursor solution was prepared by physical blend of xanthan gum (XG) and methylcellulose (MC) in aqueous solution. Due to the formation of XG network composed of XG double helical strand structure, XG/MC blend was a high viscous solution with good shear-thinning property at room temperature. When the temperature was changed from 23 to 37 °C, thermo-responsive MC network formed, which caused XG/MC blend solution to gelate. The gelation time and storage modulus of the blend can be tuned by XG and/or MC concentrations. Both in vitro and in vivo investigations revealed that the blend solution immediately recovered its high viscosity and rapidly formed hydrogel at body temperature after injection using a syringe. In vivo biocompatibility and biodegradability of the hydrogel were validated by implantation of the hydrogel in rats. In vitro investigation demonstrated that XG/MC blend is a promising injectable hydrogel material for long-term drug delivery.

1. Introduction

Injectable hydrogels have attracted much attention in biomedical field, such as drug delivery, cell encapsulation and tissue engineering (Li, Rodrigues, & Tomas, 2012; Lv et al., 2014; Van Vlierberge, Dubrueil, & Schacht, 2011) because they can be administrated in a minimally invasive manner and can easily fill arbitrary shaped defects (Yu & Ding, 2008). Shear-thinning injectable hydrogels and high viscosity hydrogel precursor solutions can flow under a shear stress and recover its mechanical properties on removal of the stress, therefore, they can avoid the leakage of the hydrogel precursor solution from injection site (Gutowska, Jeong, & Jasionowski, 2001; Guvendiren, Lu, & Burdick, 2012; Lu, Charati, Kim, & Burdick, 2012). Various shear-thinning injectable hydrogel systems have been reported in the literature, such as supramolecular hydrogels, peptide hydrogels and blend hydrogels (Guvendiren et al., 2012; Li & Loh, 2008). Blend hydrogels can combine two or more components with complementary properties together. For instance, Shoichet et al. developed an injectable blend hydrogel system composed of hyaluronic acid (HA) and methylcellulose (MC) for drug and cell deliveries (Caicco et al., 2013; Gupta, Tator, & Shoichet, 2006). HA/MC blends could form hydrogels at room temperature due to the dehydration of MC induced by the carboxylic groups of HA; the hydrogels had a shear-thinning property and a higher modulus post-injection due to the entangled random coil structure of HA and the thermal gelation property of MC, respectively. The blend hydrogels possess the advantages of low cost, easy preparation and improved properties. However, to the best of our knowledge, few blend hydrogels with shear-thinning property have been reported until now. In addition, for widespread biomedical applications of shear-thinning injectable hydrogels, further improvements in mechanical properties, stability, biocompatibility, biodegradability, as well as tunable gelation and self-healing kinetics are required (Guvendiren et al., 2012).

MC is a methyl modified cellulose in the C2, C3 and C6 positions of the anhydroglucose repeat unit (Arvidson et al., 2013), and is widely used in pharmaceutics. When the degree of substitution (DS) of the methyl groups in the repeat unit is between 1.6 and 2.1, MC is water soluble at low temperature, whereas phase separation and gelation occur at elevated temperature (Lott, McAllister, Arvidson, Bates, & Lodge, 2013). The sol−gel transition temperature of MC aqueous solution is about 40–50 °C; the transition temperature lowers when increasing DS and MC concentration as well as adding salting-out salt, such as NaCl, into the solution (Van Vlierbergh et al., 2011; Xu, Wang, Tam, & Li, 2004).

Xanthan gum (XG) is a biocompatible and biodegradable anionic polysaccharide produced commercially by bacterial fermentation (Bejenariu, Popa, Dulong, Picton, & Le Cerf, 2009). XG consists of a linear β-(1→4)-d-glucose backbone, which is the same as...
cellulose. Every alternate glucose residue has a charged trisaccharide side chain consisting of β-d-mannose-(1,4)-β-d-glucuronic acid-(1,2)-α-d-mannose. The internal mannose unit may be acetylated in C-6 position and the terminal mannose may carry pyruvate residues linked in 4- and 6-positions (Bejanariu et al., 2009; Le & Turgeon, 2013). In aqueous solution, XG adopts two different conformations: an ordered and rigid double helical strand structure at low temperature and a disordered and flexible coil structure at high temperature (Roy et al., 2014). The midpoint transition temperature (Tm) is about 40–50 °C depending on ionic strength (Chantaro, Pongsawatmanit & Nishinari, 2013). When the temperature of XG solution is below its Tm, the ordered double helical strand structure forms three-dimensional network, thus XG solution exhibits a weak gel-like behavior and a shear-thinning property under stress (Iijima, Shinozaki, Hatakayama, Takahashi, & Hatakayama, 2007; Zhang et al., 2015). Dyondi et al. prepared an injectable hydrogel by physical blend of gelan gum and XG as a tissue engineering scaffold for multiple growth factor delivery for bone regeneration (Dyondi, Webster, & Banerjee, 2013).

XG has a good shear-thinning property and MC has a thermal gelation property. Herein, we produced injectable hydrogel pre-cursor solution with high viscosity and excellent shear-thinning property at room temperature by blending XG and MC in pH 7.4 phosphate buffered saline solution (PBS, 10 mM phosphate buffer containing 0.15 M NaCl). The gelation properties of XG/MC blend with various XG and MC concentrations as well as the hydrogel structure were carefully characterized. The gelation mechanism was proposed. The biocompatibility and degradability of XG/MC hydrogel were validated both in vitro and in vivo. Drug loading and in vitro release were investigated. This study demonstrated that XG/MC blend is a promising injectable hydrogel material for drug delivery.

2. Experimental

2.1. Preparation of XG, MC and XG/MC blend solutions

XG (viscosity 800–1200 cps, from xanthomonas campestris) and MC (viscosity 15 cps, Mw 14 kDa, DS 1.5–1.9) were purchased from Sigma. XG solution was prepared by slowly adding XG powder into 25 mL PBS with vigorous stirring until complete dissolution and then keeping the solution at 4 °C overnight with gentle stirring. MC solution was prepared as described in the literature (Tate, Shear, Hoffman, Stein, & LaPlace, 2001). XG/MC blend solution was prepared by adding XG powder into MC solution followed by overnight vigorous stirring and then 24 h gentle stirring at 4 °C. After removal of bubbles by centrifugation at 2000 rpm for 6 min, transparent XG/MC blend solution was obtained. The final XG concentration in the blend solution was 1 wt%, 2 wt% or 3 wt%, indicated as XG1, XG2 or XG3; the final MC concentration in the blend solution was 8 wt%, 10 wt% or 12 wt%, indicated as MC8, MC10 or MC12. Various samples including individual XG and MC solutions and XG/MC blend solutions with different XG and MC concentrations are summarized in Table S1 of Supplementary data. All the samples were stored at 4 °C before use.

2.2. Rheological measurements

Rheological measurements of various XG, MC and XG/MC blend samples were performed on a stress-controlled HAAKE MARS III rheometer (Thermo Fisher) with a cone-plate geometry (angle: 2°; diameter: 60 mm; gap: 0.105 mm). Silicone oil was carefully applied to seal the cone-plate during the measurement. The mechanical properties of the samples were measured at 5 Pa stress and 10 rad/s frequency within the linear viscoelastic region. Oscillation amplitude sweep and frequency sweep were applied to measure the storage modulus (G’) and loss modulus (G”) of the samples at 37 °C. Temperature sweep from 15 to 45 °C at a heating rate of 1 °C/min was carried out to measure gelation temperature. Time sweep at 37 °C was performed to investigate the gelation kinetics. The shear-thinning properties of the samples were investigated by steady rate sweep at 23 and 37 °C, and the viscosities of the samples were measured as a function of shear rate. Step-rate time-sweep was performed to investigate the thixotropic recovery properties of the samples between low shear rate (0.1 s⁻¹) and high shear rate (10 s⁻¹) at 23 °C, and also between low shear rate (0.5 s⁻¹) and high shear rate (500 s⁻¹) at 37 °C.

2.3. FTIR, XRD and CD (circular dichroism) measurements

FTIR measurements of the freeze-dried hydrogel samples were conducted on a Nicolet 6700 FTIR spectrometer (Thermo Fisher). XRD patterns of the freeze-dried hydrogel samples were acquired using a X’ pert PRO X-ray powder diffractometer (PANalytical). UV CD spectra of XG, MC and XG/MC blend solutions were recorded on a MOS 450 CD spectrometer (Bio-Logic Science Instruments) at 23 °C. XG concentration was 2 mg/mL and MC concentration was 10 mg/mL in the CD samples.

2.4. In vitro degradation and swelling

The degradation and swelling behaviors of XG/MC hydrogel samples in 37 °C PBS were investigated as reported in the literature (Gupta et al., 2006; Lee et al., 2013). Briefly, 3 mL PBS was added into each of the tubes containing 1 mL hydrogel and then the tubes were incubated at 37 °C. The PBS was changed daily. At a predetermined interval, the hydrogel sample was lyophilized and weighed. The percent of remnant dry weight was calculated using the following equation: Remnant dry weight (%t) = Wd/Wa × 100%, where Wd and Wa are the dry weights of the hydrogel samples after t and days of the incubation, respectively. The swelling ratio was also measured by immersion of the hydrogel samples in 37 °C PBS. At a predetermined interval, the wet weight of the hydrogel sample was determined and the swelling ratio was calculated using the following equation: Hydrogel swelling ratio (%t) = (Ww − Wd)/Wd × 100%, where Ww is the initial weight of unswollen hydrogel sample and Wd is the wet weight of the sample after t days of the immersion.

2.5. In vivo biocompatibility and elimination evaluations

The animal experiments of this study were performed at Experimental Animal Center of School of Pharmacy of Fudan University in full compliance with the guidelines approved by Shanghai Administration of Experimental Animals. Male SD rats (about 220 g) were subcutaneously injected in the backside with 0.5 mL XG2/MC10 blend solution using a syringe having 23G needle. At a predetermined interval, the rats were sacrificed, the injection sites were carefully opened and photos were taken. The tissues around the implanted hydrogels were surgically taken out, fixed, dehydrated and embedded in paraffin in succession. The specimens were cut into 4 μm thick sections and the sections were stained with hematoxylin–eosin (H&E) to examine the inflammatory responses of the hydrogel in rats.

2.6. Drug loading and in vitro release

Doxorubicin (DOX) aqueous solution with pH 7.4 was mixed with XG/MC blend solution to prepare DOX/XG2/MC10 blend. The solution was equilibrated at 4 °C for 48 h and subsequently was centrifuged at 2000 rpm for 6 min to remove bubbles. The final DOX concentration in the blend solution was 0.5 or 1 mg/mL.
In vitro DOX release of DOX/XG2/MC10 hydrogel in 37°C PBS was investigated in triplicate. Briefly, 10 mL PBS was added into a vial containing 1 mL DOX/XG2/MC10 hydrogel and the vial was incubated in a shaking water bath at 37°C. Periodically, 3 mL of the release medium was taken out and 3 mL fresh PBS was added. The DOX concentration in the release medium was determined as previously reported (Hao, Ma, Huang, He, & Yao, 2013).

3. Results and discussion

3.1. Rheological properties of XG/MC blend

In this study, we blended XG and MC in PBS to prepare injectable hydrogel. We used rotational rheometer to investigate the rheological properties of the samples listed in Table S1 of Supplementary data. Compared with XG weak gel-like samples, MC and XG/MC blend hydrogels present broader linear viscoelastic region at 37°C, and the stress applied to break the network structure of MC and XG/MC hydrogel samples is larger than 100 Pa (Fig. S1, Supplementary data). Fig. 1 shows frequency-dependent rheological results acquired in the linear viscoelastic region. For all the samples, the G′ values exceed the respective G″ values in the measured frequency range at 37°C, confirming the formation of the hydrogels. XG samples exhibit a weak-gel behavior and smaller G′ and G″ values; in contrast, XG/MC samples present significantly improved G′ and G″ values at 37°C. The G′ value of XG/MC hydrogel increases with XG concentration as well as MC concentration, indicating that both XG and MC make contributions to the mechanical strength of XG/MC blend hydrogel.

Fig. 2 shows the thermo-responsive changes of G′ and G″ of various XG, MC and XG/MC samples. XG samples display weak-gel behavior and good thermal stability in the temperature range of 15–45°C. MC and XG/MC samples present thermo-responsive gelation behavior. The G′ values are smaller than the respective G″ values in the low temperature range, whereas the G′ values are larger than the respective G″ values in the high temperature range. The sol–gel transition temperature can be obtained from the cross-point of G′ and G″ as shown in Fig. 2. The data reveal that increasing XG concentration and/or MC concentration in XG/MC blend solution can effectively lower the transition temperature. For example, the transition temperatures of 8%, 10% and 12% MC samples are 36.6, 34.2 and 32.8°C, respectively; when 3% XG was blended with 8%, 10% and 12% MC, the transition temperatures decrease to 28.5, 30.2 and 28.0°C, respectively. Gupta and Shoichet et al. reported that in HA/MC system the carboxylic groups of HA decreased the gelation temperature of MC due to the dehydration of MC induced by the carboxylic groups (Gupta et al., 2006). Similarly, XG also contains carboxylic groups and thus the carboxylic groups can decrease the gelation temperature of MC in the same mechanism. The data in Fig. 2 confirm that the gelation temperatures of the XG/MC blend samples are below 37°C. Furthermore, Fig. 2 shows that increasing the temperature from the gelation temperature to 45°C, the MC and XG/MC hydrogels increase their mechanical properties as indicated by the increasing G′ values.
Results

The gelation kinetics at 37 °C of the solution samples with original temperature of 23 °C (room temperature) was investigated. For MC and XG/MC samples, their respective oscillation time curves in Fig. 3 present a crosspoint of G’ and G”, which corresponds to the gelation time at 37 °C. The gelation time value decreases effectively with the increases of XG and/or MC concentrations. For example, the gelation time values of 8%, 10% and 12% MC solutions are 357, 122 and 99 s, respectively; when 3% XG was blended with 8%, 10% and 12% MC, the values decrease to 40, 43 and 33 s, respectively. The results in Fig. 3 demonstrate that XG/MC blend solutions possess fast gelation kinetics at 37 °C.

3.2. Shear-thinning injectable properties

XG2/MC10 blend has a sol–gel transition temperature of 32.7 °C and gelation time of 48 s at 37 °C (Figs. 2 and 3). Considering that injection is usually performed at room temperature, we investigated the shear-thinning properties of XG2/MC10 at room temperature (23 °C) and body temperature (37 °C); we also applied a high shear rate to break the network structure of XG2/MC10 and then applied a low shear rate to monitor the viscosity recovery at both room temperature and body temperature. Fig. 4A shows that 2% XG (XG2/MC0) weak gel is more viscous than XG2/MC10 and 10% MC (XG0/MC10) solutions at 23 °C. In contrast, at 37 °C, XG2/MC10 blend hydrogel and XG0/MC10 hydrogel are more viscous than XG2/MC0 weak gel (Fig. 4B) due to the thermal gelation of MC. It is notable that XG2/MC0, XG2/MC10 and XG0/MC10 decrease their viscosities with the increase of shear rate at both 23 and 37 °C. Fig. 4C and D reveals that XG2/MC10 possesses excellent thixotropic recovery property at both 23 and 37 °C. XG2/MC10 immediately recovers its viscosity to 94% of the original value once changing the shear rate from high to low at 37 °C.

Fig. 4E shows that XG2/MC10 high viscous solution can be injected using a syringe with 23 G needle at room temperature, and the solution immediately formed hydrogel after injection into 37 °C PBS (photo c). XG0/MC10 solution cannot form hydrogel after the same injection (photo a), while XG2/MC0 weak gel can recover its weak-gel state after the same injection (photo b). At 37 °C, XG2/MC10 is in gel state, however, XG2/MC10 hydrogel can also be injected using a syringe with 23 G needle as shown in photo d. This advantage implies that we need not worry about the premature gelation of XG2/MC10 solution in syringe needle and XG2/MC10 blend can be successfully injected into body. The results in Fig. 4 reveal that the blend is a high viscous solution at room temperature, after injection into 37 °C medium the blend solution immediately recovers its high viscosity and forms hydrogel with improved mechanical property.

3.3. Structure analyses

Fig. 5A shows the FTIR spectra of various freeze-dried hydrogels. The characteristic peak at 2837 cm⁻¹ (C–H stretch in methyl ether) presented in MC spectrum (Rimduisit, Jingjed, Damrongrakkul, Tiptipakorn, & Takeuchi, 2008) does not change in XG/MC spectra. The peak at 1723 cm⁻¹, which represents the stretch of carbonyl of acetyl groups in XG spectrum (Maia, Silva, Curti, & Balaban, 2012), does not shift in XG/MC spectra. XG and MC hydrogels display broad bands at 3289 and 3451 cm⁻¹, respectively, related to
the O–H stretch (Maia et al., 2012; Rimdusit et al., 2008). For the various XG/MC hydrogels, the O–H stretch band shifts from 3451 to 3289 cm⁻¹ when changing the weight ratio of XG:MC from 0:1 to 1:1. The hydrogel with 1:1 ratio presents 3357 cm⁻¹ characteristic peak, which is almost the mean value of 3451 and 3289 cm⁻¹. This result indicates that the shift of O–H stretch band results from the ratio change of XG to MC in the hydrogels. The FTIR results indicate that no chemical bond forms between XG and MC.

In the XRD patterns of freeze-dried XG, MC and XG/MC hydrogels (Fig. 5B), the sharp diffraction peaks in the 2θ region of 5–80° are attributed to NaCl crystal (Kiel et al., 2012). The XG pattern does not display significant diffraction peak. The peak at 2θ = 20.4° in MC pattern is attributed to the partial crystalline structure in MC (Anirudhan, Rejeena, & Tharun, 2013); the XG2/MC10 pattern presents the same diffraction peak at 2θ = 20.4°. The XRD patterns indicate that XG molecules have no effect on MC partial crystalline structure and also MC molecules have no effect on XG noncrystalline structure in XG/MC hydrogel.

We used CD spectroscopy to investigate the conformations of XG, MC and XG/MC solutions at 23 °C. As mentioned above, XG has an ordered double helical structure in aqueous solution and the Tₘ of XG from ordered double helical structure to disordered coil conformation is about 40–50 °C (Chantaro et al., 2013). Fig. 5C shows that there is no significant absorption in the MC spectrum. The XG spectrum exhibits a maximum absorption at 205 nm and a minimum absorption at 223 nm, which are the same as reported in the literature (Bresolin, Milas, Rinaudo, & Ganter, 1998). The XG/MC spectrum exhibits a maximum absorption at 206 nm and a minimum absorption at 223 nm, which are almost the same as the XG spectrum. The CD spectra reveal that MC neither promotes nor disturbs the ordered double helical structure of XG in XG/MC blend solution.

3.4. Gelation mechanism

The studies above demonstrate that at 23 °C, XG solution possesses weak-gel and shear-thinning properties due to the three-dimensional network structure formed by the XG double helical strands, meanwhile MC solution is in liquid state with low viscosity. In XG/MC blend solution, both XG and MC keep their own structures. The blend solution presents shear-thinning behavior but its viscosity is lower than the viscosity of XG solution (Fig. 4A). This phenomenon can be explained by the fact that MC concentration is much higher than XG concentration in the blend solution, in which the XG three-dimensional network may be partly disturbed by the MC molecules. When changing the temperature from 23 °C to gelation temperature, thermoresponsive MC network forms via intermolecular hydrophobic interaction that causes XG/MC blend solution to gelate. The carboxylic groups of XG and the NaCl molecules in PBS cause the dehydration of MC that result in the decreases of MC gelation temperature and gelation time. These results reveal that XG/MC blend
Fig. 4. Shear rate-dependent viscosity changes of XG2/MC0, XG0/MC10 and XG2/MC10 samples at (A) 23°C and (B) 37°C; viscosity changes of XG2/MC0, XG0/MC10 and XG2/MC10 samples: (C) between low shear rate (0.1 s⁻¹) and high shear rate (10 s⁻¹) at 23°C, and (D) between low shear rate (0.5 s⁻¹) and high shear rate (500 s⁻¹) at 37°C; (E) photos of the injections of (a) 23°C XG0/MC10 solution, (b) 23°C XG2/MC0 weak gel and (c) 23°C XG2/MC10 blend solution into 37°C PBS, as well as (d) the injection of 37°C XG2/MC10 hydrogel using 23G needle.

contains XG network only at 23°C but possesses XG and MC double networks at 37°C. This network structure, which is illustrated in Fig. 5D, is different from the structure of injectable HA/MC blend hydrogel reported by Gupta et al. (2006). In HA/MC blend, MC was already in gelation state prior to injection. The network structure of XG/MC is also different from the structure of injectable gellan gum/XG blend hydrogel reported by Dyondi et al. (2013). In gellan gum/XG blend, hydrogel formed in the presence of Ca²⁺ ions and at the temperature below 42°C, that is, the hydrogel was already produced prior to injection. In this study, XG/MC blend contains XG network only and the blend is a high viscous solution before injection, thus, the injection of XG/MC may be easier than the injections of HA/MC as well as gellan gum/XG. After injection, the formation of XG and MC double networks at 37°C endows XG/MC blend with rapidly thermal gelation and enhanced mechanical properties.

3.5. In vitro degradation and swelling properties

In vitro degradation behaviors of various XG/MC hydrogels were investigated using a weight loss method after soaking the hydrogels in PBS at 37°C and then lyophilization. Fig. 6A shows that XG0/MC10 and XG0/MC12 hydrogels decreased about 50% and 44% of their original weights after 44 days of soaking, respectively. It was reported that the decrease of MC weight in vitro is possibly due to gel erosion (Gupta et al., 2006; Tate et al., 2001). In contrast, XG3/MC0 weak gel did not decrease its weight after 44 days of
soaking and its weight increased in the first 2 days because XG has strong water binding capacity (Vilgis, 2012). Both XG and MC have a cellulose backbone. In this study, we used 14 kDa MC, which may dissociate from the hydrogel surface that increases the erosion rate. XG has double helical structure that may decrease the erosion rate. The erosion rates of XG/MC hydrogels are not sensitive to XG concentration; the rates of XG2/MC10 and XG3/MC12 hydrogels are similar to the rates of XG0/MC10 and XG0/MC12 hydrogels. The reason may be that in XG/MC hydrogels the XG concentration is much lower than the MC concentration. The swelling ratios of the XG/MC hydrogels after soaking in PBS at 37 °C are presented in Fig. 6B. XG weak gel swelled more than MC hydrogel samples; the swelling ratio increased with XG concentration in XG/MC hydrogels during the first 9 days of soaking; subsequently, MC and XG/MC hydrogels decreased their swelling ratios because of the erosion shown in Fig. 6A. The SEM images (Fig. S4 of Supplementary data)

Fig. 5. (A) FTIR spectra of various freeze-dried XG/MC hydrogels; (B) XRD patterns of freeze-dried XG2/MC0, XG0/MC10 and XG2/MC10 hydrogels; (C) CD spectra of 2 mg/mL XG solution, 10 mg/mL MC solution, and XG/MC blend solution containing 2 mg/mL XG and 10 mg/mL MC measured at 23 °C; (D) illustration of the gelation mechanism of XG/MC blend solution.

Fig. 6. (A) Percent of remnant dry weights and (B) swelling ratios of various hydrogels after soaking in PBS at 37 °C.
show that all the MC, XG and XG/MC hydrogels contain more and larger pores after erosion.

3.6. In vivo gelation, elimination and biocompatibility

XG2/MC10 high viscous solution was subcutaneously injected in the backside of male SD rats at room temperature using a syringe with 23 G needle. The photo taken at 30 min post-injection (Fig. 7A, Day 1) confirms the formation of XG2/MC10 hydrogel in vivo. Fig. 7A shows that the hydrogel increased its volume from day 1 to day 7 post-injection due to the swelling, which has been proved in Fig. 6B, after that the volume decreased gradually. The hydrogel disappeared completely after 36 days of the injection, which is much faster than the erosion in vitro (Fig. 6A). Possibly, the degradation in vivo (Kim, Won, Lim, & Kim, 2012) accelerates the elimination of the hydrogel. There was neither any observable abnormality on the skin surfaces nor any sign of edema, redness or tissue necrosis in the surrounding tissues of the implanted hydrogel, indicating that the hydrogel does not induce extensive inflammatory response. The histological images (Fig. 7B) show inflammatory cells in the tissues around the implanted hydrogel. The images display that the inflammatory cells decrease with the increase of implantation time. On day 27 post-injection, the inflammatory cells almost disappeared. On day 37 post-injection, the histology of the surrounding tissues recovered completely. The in vivo investigation demonstrates that XG2/MC10 is an injectable, biocompatible and biodegradable hydrogel material.

3.7. Doxorubicin (DOX) loading and in vitro release

DOX, an anthracycline anticancer drug, was loaded into hydrogel by simply mixing DOX with XG2/MC10 blend solution at room temperature. The sol–gel transition temperature of DOX/XG2/MC10 blend is 32.5 °C, as shown in Fig. S6 of Supplementary data. The gelation time value of DOX/XG2/MC10 at 37 °C is 61 s (Fig. S7 of Supplementary data). These results indicate that the drug loaded XG2/MC10 solution also has good thermo-responsive gelation property at 37 °C.

In vitro DOX releases from the hydrogels in 37 °C PBS are shown in Fig. 8. DOX/XG2/MC10 hydrogels present sustained release behavior. The accumulative release of DOX depends on the DOX concentration in the hydrogel. Higher DOX concentration in the hydrogel results in longer release. Fig. 7A shows that XG2/MC10 hydrogel disappeared completely after 36 days of implantation. Compared with the release in vitro, we can expect that the loaded DOX can be released faster via hydrogel degradation in vivo. The results in Fig. 8 indicate that the hydrogel can be used as a long-term drug delivery material.
Fig. 8. Accumulative releases of DOX in 37 °C PBS from DOX/XG/MC10 hydrogels containing 0.5 and 1 mg/mL DOX.

4. Conclusions

In this study, we used commercial polysaccharides, XG and MC, and physical blend method to produce injectable, biocompatible and biodegradable hydrogel. XG solution exhibits a weak-gel behavior with good shear-thinning property; MC solution is a low viscous solution at room temperature and gelates at body temperature. XG/MC blend hydrogel, which is composed of XG and MC double networks, combines the advantages of XG and MC together. XG/MC blend is a high viscous solution with good shear-thinning property at room temperature; the blend immediately recovers its high viscosity and forms hydrogel at body temperature after injection. The gelation temperature and gelation time of the blend solution at 37 °C can be tuned by XG and MC concentrations. The storage modulus of the blend hydrogel can also be adjusted by XG and MC concentrations. XG/MC hydrogel is biocompatible and biodegradable in rat body. DOX can be loaded into hydrogel by simply mixing DOX with XG/MC blend solution at room temperature, and the loaded DOX can be released from the hydrogel sustainedly. This study demonstrates that XG/MC blend is an injectable, biocompatible and biodegradable hydrogel material for long-term drug delivery.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2015.06.013

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