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One-step fabrication of biocompatible carboxymethyl cellulose polymeric particles for drug delivery systems

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ABSTRACT

Carboxymethyl cellulose (CMC) particles were synthesized in one step employing inverse micelle microemulsion polymerization using divinyl sulfone as crosslinking agent. These synthesized particles were further modified and demonstrated as drug delivery system. Acyclovir was chosen as the model drug. The synthesized CMC particles were made magnetic responsive by encasing independently prepared magnetic ferrite particles (Fe_3O_4) in CMC polymeric particles during the synthesis as magnetic-CMC (m-CMC). The particles were characterized by using dynamic light scattering (DLS), zeta potential measurements (ZP), FT-IR spectroscopy, scanning electron microscopy (SEM) and thermogravimetric analyzer (TGA). The synthesized particles have wide size distribution ranging from 100 to 10,000 nm. The further modification of CMC and magnetic Fe_3O_4 containing CMC polymeric particles crosslinked at different ratios was performed successfully by introducing new functional groups to the CMC networks. It was determined that these particles obtained from the natural CMC polymers have a potential range of application as drug and targeted drug delivery system in biomedical field.

1. Introduction

Currently, controlled drug release techniques have attracted much attention due to their advantages to the conventional forms of dosage, such as prolonging the release time, and decreasing the poisoning effect reducing the drug release rate (Peng, Zhao, & Gao, 2010; Rosenau et al., 2009).

Polysaccharides are regarded as the most popular polymeric materials to prepare nanoparticles for drug delivery systems They have received a lot attention and been recognized to be the most promising materials because of their outstanding merits, such as being abundant, cheap, safe and their easily modified characteristics (Baumann, Liu, & Faust, 2003; Liu, He, Durham, Zhao, & Roberts, 2008; Liu, Jiao, et al., 2008). Recently, cellulose-based superabsorbent hydrogels have been prepared through etherifying of the cellulose with succinic anhydride, which can absorb an amount of water that is around 400 times of its dry weight (Yoshimura, Matsuo, & Fujioka, 2006) and another one was used as a protein carrier which was prepared by using epichlorohydrin (ECH) as crosslinker (Chang, Duan, Cai, & Zhang, 2010).

Carboxymethyl cellulose is a water-soluble polysaccharide possessing both carboxylate and hydroxyl groups that allow this "green" and inexpensive polysugar to exert strong interactions with metal particles (Liu, He, Gunn, Zhao, & Roberts, 2009; Rogers, Kamitakahara, Yoshinaga, & Takano, 2010). Amongst the cellulosic ethers, carboxymethyl celluloses are very important derivatives of cellulose; they have good solubility, high chemical stability, and they are safe, non-toxic, hydrophilic, biocompatible, and biodegradable. Moreover, polysaccharides come from renewable resources in nature and have habitually economical advantages over synthetic polymers. Cellulose derivatives, especially carboxymethyl cellulose sodium salt (CMCNa) has been found in numerous applications in a variety of fields, including the paper and textile, food, cosmetics, chemical, and pharmaceutical industries (Song, Zhou, Li, Guo, & Zhang, 2009) as both stabilizing and reducing reagent (He, Liu, Roberts, & Zhao, 2009; He, Zhao, Liu, & Roberts, 2007; Liu, He, et al., 2008; Liu, Jiao, et al., 2008; Vimala, Sivudu, Mohan, Sreedhar, & Raju, 2009; Xiong, Zhao, & Pan, 2009).

Carboxymethyl cellulose is a biocompatible macromolecule that has been used for drug delivery systems in many investigations with the aim of controlled drug release with various ways: it has been used for a microgel matrix for a new type of sticking plaster; due to its adhesive characteristic it has been used as bioadhesive material, especially as mucoadhesive polymer for nasal (Tas et al., 2009) and buccal (Shanker, Kumar, Gonugunta, Kumar, & Veerareddy, 2009) drug delivery systems.

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Magnetic nanoparticles have been investigated for gene separation in biochemical products and cells, and/or acted as the magnetic guidance of particle systems for specific purposes such as drug delivery, owing to their magnetic properties being different from those of their bulk material counterparts. There are also studies of superparamagnetic oxide as a contrasting agent for magnetic resonance imaging and it has been investigated extensively over the past decade (Huang & Tang, 2004). Small metallic particles are prone to aggregations. There are many investigations for magnetite that are encapsulated into some sort of matrices such as polymers, surfactants were used to prevent their coagulation induced by the magnetic dipolar attraction and improve their chemical stability (Barrera, Herrera, & Rinaldi, 2009). Soapless emulsion polymerization (Sacanna & Philipse, 2006; Wang, Chiu, Lee, & Young, 2004), miniemulsion polymerization (Ramírez & Landfester, 2003), conventional emulsion polymerization (Xu, Friedman, Humfeld, Majetich, & Asher, 2002), and inverse emulsion polymerization (Deng, Wang, Yang, Fu, & Elaïssari, 2003) and so on are the mostly employed techniques to prepare magnetite/polymer composite particles.

In this study, the carboxymethyl cellulose (CMC) and magnetic carboxymethyl cellulose (m-CMC) particles were synthesized by microemulsion polymerization in sodium bis(2-ethylhexyl)sulfosuccinate (AOT) as reverse micelle forming surfactant as the template, and divinylsulfone (DVS) was used as the crosslinker. The magnetic responsive behaviors were obtained by the encapsulation of metal nanoparticles inside crosslinked CMC during particle synthesis. Additionally, the chemical modification of the particle system was carried out to introduce new functional groups. The structural characteristics of the particles were examined by scanning electron microscope (SEM), transmission electron microscopy (TEM), zeta potentiometer, dynamic light scattering (DLS), FT-IR, elemental analyzer, thermogravimetric analysis (TGA). For the drug delivery potential of these particles, acyclovir was used as a model drug and the release characteristics of them were investigated via UV–Vis spectrometer.

2. Experimental

2.1. Materials

The materials used for non-magnetic particle synthesis are carboxymethyl cellulose sodium salt (CMCNa, viscosity 400–1000 mPa s, average M_w ~250,000, degree of substitution 1.2, Sigma), divinylsulfone (DVS, >98%, Merck), sodium bis(2-ethylhexyl)sulfosuccinate (AOT, 96%, Fluka), and 2,2,4-trimetylpentane (isooctane, 99%, Sigma). For magnetic nanoparticle (Fe_3O_4) synthesis, ferric chloride ($FeCl_3{\cdot}6H_2O$, Across Organics), ferrous chloride ($FeCl_2{\cdot}4H_2O$, Fluka), ammonium hydroxide (NH_3, H_2O, 26%, Riedel-de Haën), and oleic acid (OA, Fisher Scientific) were used. 3-Chloro-2-hydroxypropyltrimethylammonium chloride (CHPTAC, 65%, Sigma) was used for the modification of CMC particles. For drug release, dialysis tubing cellulose membrane (retains >90% of cytochrome C (M.W. 12,400) in solution over a 10-h period, Sigma–Aldrich) was used. All of the chemicals were used without further purification. Methanol (99.9%, Merck), ethanol (99.5%, J.T. Baker), and the model drug acyclovir was obtained from a local vender. The PBS was prepared in DI water using NaCI (0.14 M), KCI (2.68×10^{-3} M), Na_2HPO_4 (0.01 M), KH_2PO_4 (1.76×10^{-3} M).

2.2. Synthesis of CMC particles

CMC particles were synthesized using water-in-oil microemulsion system. The system which consists of 0.50 ml CMCNa solution (50 mg CMCNa per ml in 0.2 M NaOH) was dispersed in 15 ml isooctane containing 0.2 M AOT. The mixture was vortexed until a clear solution was obtained. After DVS (50–100 mol% relative to the CMCNa repeating unit) was added as a crosslinking agent to this mixture, it was allowed to stir for 1 h at ambient temperature with a stirring speed of 1200 rpm. To collect the CMC particles, the reaction mixture was decanted after precipitated in acetone for one night. The precipitate was washed with acetone–water mixture and collected by centrifugation at 10,000 rpm (20 °C) for 10 min (it was repeated 3 times). The products were dried in an oven at 40 °C to a constant weight. If not stated otherwise, 50% DVS (based on repeating unit of CMC) was used throughout this investigation.

To separate particles by size via centrifugation, the CMC particles were dispersed in acetone–water (1:5, v/v) mixture and collected by centrifugation at different rates, e.g., 1000, 4000, and 10,000 rpm (20 °C) for 10 min. Again, the products were precipitated in acetone and then dried in an oven to a constant weight at 40 °C, and stored in a closed container for drug loading and release studies.

2.3. Synthesis of Fe_3O_4–CMC composite particles (m-CMC)

Magnetic nanoparticles were prepared to Massart's method (Massart, 1981). For the magnetic nanoparticles synthesis, 0.22 g $FeCl_2{\cdot}4H_2O$ and 0.61 g $FeCl_3{\cdot}6H_2O$ were dissolved in distilled water (30 ml). The mixture was vigorously stirred under nitrogen gas at 50 °C and 2.5 ml aqueous ammonia (26%) was added slowly into the solution under vigorous stirring to obtain a good dispersion of the particles. This mixture was centrifuged at 5000 rpm for 5 min then washed with water 3 times. After the last centrifugation 30 ml water was added to the tube, the mixture was vortexed, and 1 ml oleic acid (OA) was added to this mixture.

The method of Fe_3O_4–CMC particle synthesis is the same with the CMC particle synthesis mentioned above. For embedding the magnetic nanoparticles inside CMC, a freshly prepared mixture including Fe_3O_4 with an amount of 100 μl was added to the CMC precursor before DVS addition.

2.4. Modification of CMC particles

For the modification of CMC particles two mixtures were prepared. An adequate amount of NaOH (0.2 M) was added to the first mixture in a 100 ml beaker and previously prepared crosslinked CMC particles were added into it with a stirring speed of 400 rpm for 2 h at 25 °C. As the second mixture, a certain amount of CHPTAC aqueous solution was added into the NaOH solution in another beaker and the mixture was stirred at the same speed, temperature and time. The second mixture was added into the first mixture vessel and stirred for 12 h. After that step, the reaction product was neutralized with aqueous HCl. Then, the reaction mixture was precipitated in ethanol. The precipitate was washed with ethanol–water mixture and collected by centrifugation at 10,000 rpm for 10 min (the washing was repeated 3 times). The products denoted as quaternized-CMC (QCMC) were dried in an oven at 40 °C to a constant weight.

2.5. Measurement

CMC particles were visualized by using scanning electron microscopy (SEM, Jeol JSM-5600 LV). The powdered CMC samples were placed on an aluminum stub and prepared for SEM observation with depositing gold to a few nm thicknesses to enhance the surface conductivity. TEM (JEM 1220) analysis was performed on m-CMC particles suspended in ethyl alcohol and dispersed in formwar coated Cu TEM grids.

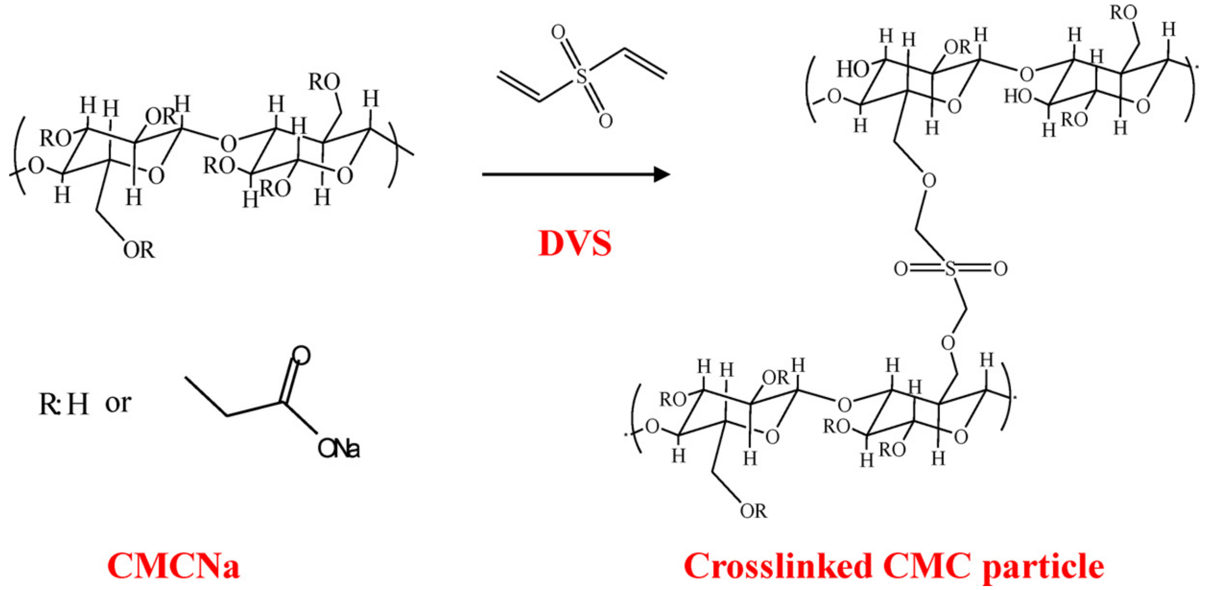

Fig. 1. Schematic illustration of CMC particle synthesis.

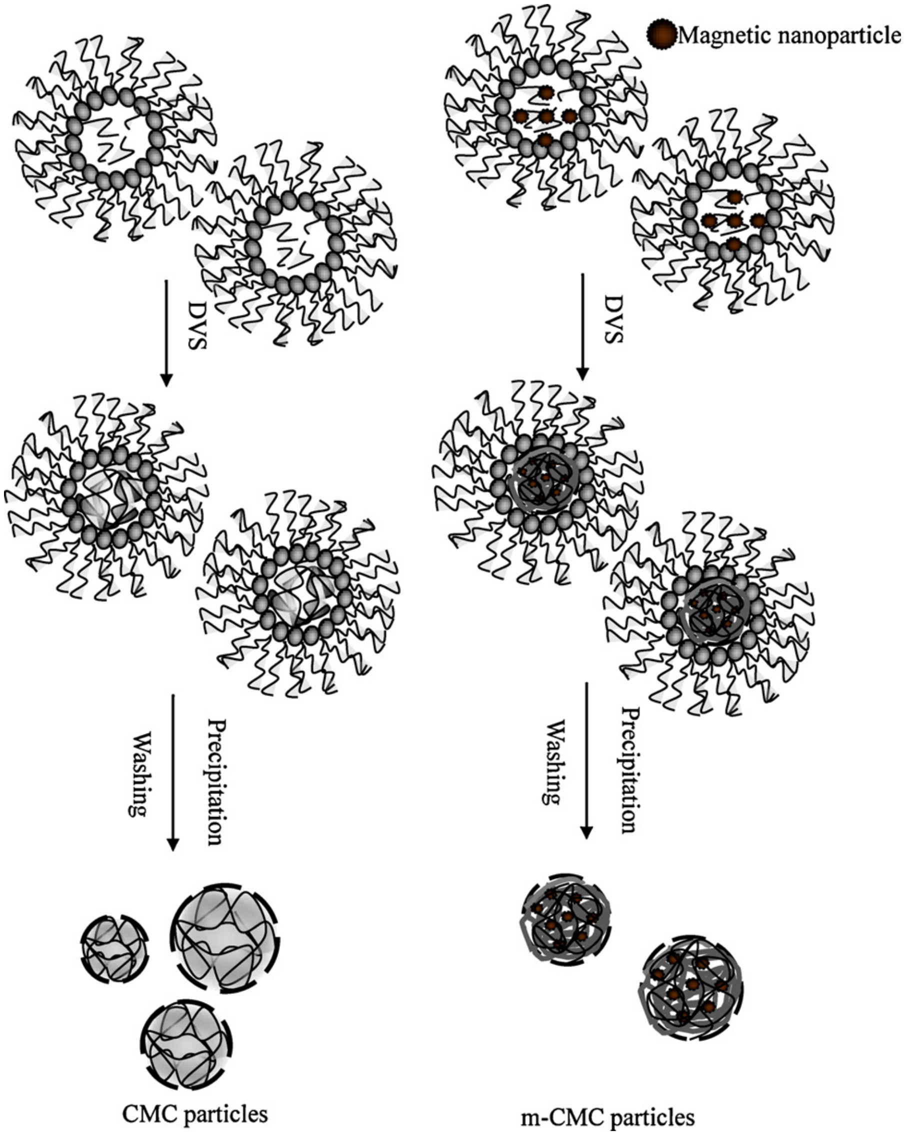

Fig. 2. Schematic illustration of CMC and magnetic CMC (m-CMC) particle synthesis in AOT reverse micelles.

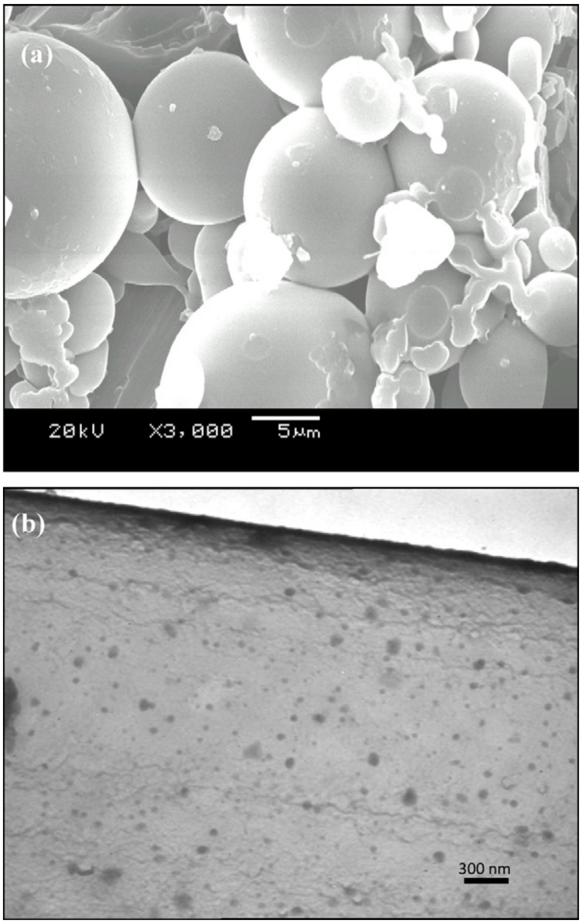

Fig. 3. (a) SEM image of CMC particles, and (b) TEM image of m-CMC particles synthesized in inverse emulsion system at ambient temperature using DVS as cross linking agent.

FT-IR spectra of samples were performed with an ATR Fourier Transform Infrared Spectrometer (Perkin Elmer Spectrum 100) with 4 cm^{-1} resolution.

Elemental Analysis (Leco SL-144 DR) was used for investigating the existence of sulfur coming from DVS to confirm the cross-linkage of the polymer structure in the particle.

The zeta potential of the particles was determined using Zetasizer (Nano Series, Model # ZEN 3600). The particles were dispersed in distilled water before this measurement. Hydrodynamic diameter and the polydispersity index of the particles were performed with dynamic light scattering (DLS) using particle size analyzer (Brookhaven Ins. Corporation 90 plus) by suspending the particles in distilled water at room temperature.

Magnetic content of m-CMC composite particles was investigated by thermogravimetric analyzer (TGA, SII TG/DTA 6300 Japan). TGA was performed under N_2 atmosphere at the rate of 100 ml min^{-1}. The temperature range was between 50 °C and 1000 °C with a heating rate of 10 °C min^{-1}.

Drug loading and releasing studies were carried out by using UV–Vis spectrometer (UV-Vis Spectrometer, T80$^+$) at 251 nm wavelength.

2.6. Drug loading and in vitro drug release

A weighted amount (400 mg) of particles was partially loaded with an antiviral drug, acyclovir (Ac), by soaking the particles in 140 ml 400 ppm Ac solution in methanol for 24 h with a 500 rpm stirring speed. After loading, particles were purified by centrifugation and dried at 40 °C in an oven. Then, 100 mg Ac loaded dry CMC particles were taken into a cleaned cellulose membrane with 3 ml phosphate buffer saline (PBS, pH 7.4). The in vitro drug release from these particles was studied in PBS (total PBS volume is 100 ml) at room temperature. While the solution was stirred with a speed of 150 rpm, the release medium was withdrawn at specific time intervals and the Ac content in solution medium was determined by UV spectrometer at 251 nm via a previously formed calibration curve in PBS at the same wavelength.

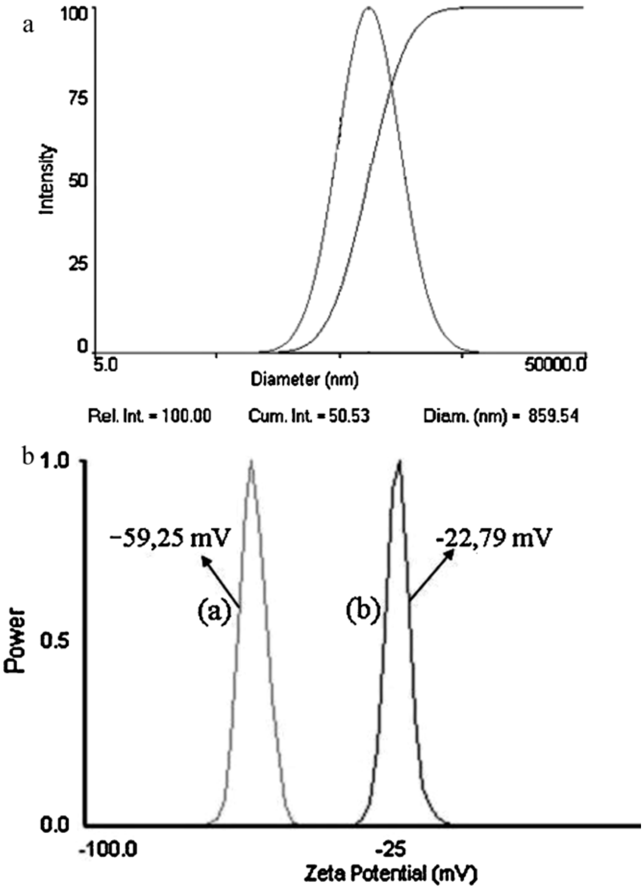

Fig. 4. (a) Particle size distribution of CMC particles dispersed in distilled water, (b) zeta potential measurement of CMC (a) and QCMC (b) particles dispersed in distilled water.

The particles of different sizes separated by centrifugation (at 1000, 4000, 10,000 rpm) were loaded with Ac as the same procedure above, but this time loading solution was refreshed three times in order to increase loading amounts of Ac at every 8 h. Total amount of loaded Ac was calculated by using UV spectrometer. Then, 100 mg Ac loaded dry CMC particles were taken into a cleaned cellulose membrane with 3 ml PBS and the membrane was immersed into 97 ml PBS containing vessel. The release medium was withdrawn at specific time intervals and the Ac content in solution medium was determined by UV.

3. Results and discussion

3.1. Synthesis and characterization of particles

CMC particles were synthesized using water-in-oil microemulsion systems using AOT in a similar way as reported earlier in the hyaluronic acid particle preparation (Sahiner & Jia, 2008). Fig. 1 represents the particle synthesis process via crosslinking of linear CMCNa. The particles were characterized after crosslinking CMCNa

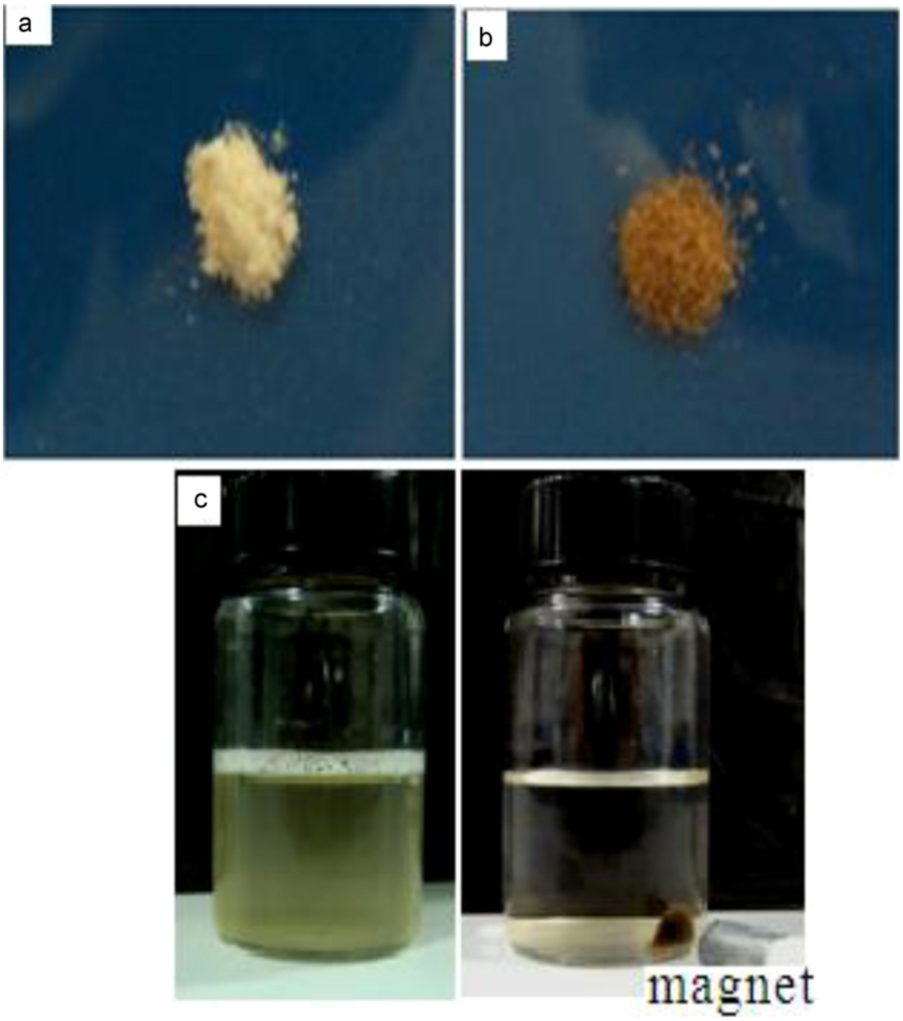

Fig. 5. Digital images; (a) CMC particles, (b) magnetic CMC particles, and (c) magnetic CMC particles dispersed in water.

with DVS. The elemental analysis result confirmed the existence of sulfur coming from DVS that was used in particle formation. The sulfur content increased from 0 to 3.64 wt% for linear CMC and CMC particle after crosslinking reaction and the C content was decreased from 40.364 to 26.631 by the introduction of DVS groups in the structures.

Magnetic Fe_3O_4 containing CMCNa as composite materials with magnetic properties were also prepared by including separately prepared magnetic Fe_3O_4 particle inside AOT reverse micelle system in the presence of linear CMCNa as illustrated in Fig. 2.

As demonstrated in SEM images (Fig. 3(a)) the CMC particles that are spherical shaped with different diameters in a very wide range (between 100 nm and 10 μm) were obtained. The particles were not filtrated before imaging to acquire the true information about the CMC particles. It is important to note that this particle can be separated to different sizes by simple filtration of centrifugation for different potential uses, e.g., drug carrier or genetic material payloads. The TEM images clearly show the existence of Fe_3O_4 particles that are distributed in CMC particles as illustrated in Fig. 3(b).

Dynamic light scattering measurements also revealed that the particle has wide size distribution with even after filtration (syrnringe filter) 860 nm mean hydrodynamic diameter as illustrated in Fig. 4(a). In order to determine the zeta potential of the particles, 1% aqueous suspension of the particles was prepared and zeta potentials were measured in DI water. Zeta potentials of CMC particles were measured as −59.25 mV as shown in Fig. 4(b), and the zeta potentials of QCMC particles obtained after the modification of CMC particles were measured as −22.79 mV (Fig. 4(b)). Zeta potential measurement results indicate that the negative charge of CMC particles was decreased by modification (quaternization) with CHPTAC as an indication of new functional group formation. The reason for not having zero charges for QCMC particles is that it is not possible to have positive charge for every carboxylic acid groups in structure (not 100% quaternization). However, the reduction from −59.25 mV to −22.79 mV clearly demonstrated that the positive charges were successfully generated. The FT-IR evaluation of both CMC and QCMC corroborates the positive charge formation by chemical modification on the particle surfaces. According to the FT-IR spectrum of CMC particles (Supplemental Fig. 1(a)), the wide peak observed at ∼3400 cm^{-1} was due to –OH stretching, while peak at ∼2922 cm^{-1} was due to asymmetric $–CH_2$ stretching, peak at 1590 cm^{-1} due to $–COO^-$ asymmetric stretching, peak at 1413 cm^{-1} due to $–COO^-$ symmetric stretching, peak at 1038 cm^{-1} due to –CO stretching (RCH_2OH). In the spectrum of QCMC particles (Supplemental Fig. 1(b)), an increase in the peak intensity due to –OH stretching was observed at ∼3400 cm^{-1} (with the effect of –OH present in CHPTAC group). The peak at ∼1700 cm^{-1} was due to –COO asymmetric stretching, while a small peak at ∼1480 cm^{-1} was due to $^+N–CH_3$, the peak at ∼1410 cm^{-1} due to C–N and since symmetric stretching is overlapping with the peak zone, the peaks are not intense.

CMC particles with magnetic properties as composites were prepared as mentioned earlier in a similar way of CMC particle preparation with the exception of just magnetic metal nanoparticle inclusion inside AOT reverse micelle before the addition of DVS. The digital photographs of the CMC and m-CMC particles are shown in Fig. 5(a) and (b), respectively. On the other hand, the (c) and (d) of the same figure demonstrate the behavior of m-CMC particle dispersion in water, under an externally applied magnetic field. It was observed that the magnetic particles were guided/directed with a magnet and accumulated on the surface of the vial. The advantage of the magnetic field responsive behavior of the particles is that they could be very useful for many applications such as directing, guiding and carrying certain species to the targeted zone.

In order to determine the magnetic metal contents of m-CMC particles, thermal gravimetric analysis of the samples was performed by CMC and m-CMC under nitrogen atmosphere up to 1000 °C and their percentage of weight loss (TG%) against the temperature is graphed and illustrated in Supplemental Fig. 2. As can be seen both particles resulted in similar degradation characteristic and the difference at 1000 °C is 5.1 wt%. Therefore, the magnetic particle content of m-CMC particles is 5.1 wt%. It is also noteworthy to mention that one can control the magnetic particle content of the m-CMC by simply adding more magnetic material during synthesis.

3.2. Drug loading and in vitro drug release

Acyclovir (Ac), which is effective on herpes viruses, with low toxicity, preventing viral DNA synthesis, and widely used in antiviral therapy was chosen as the model drug for the absorption and release studies from CMC particle as drug delivery system. The chemical structure of Ac is given in Fig. 6(a). The drug from its methanol solution was loaded to the CMC particles for 24 h. The loading efficiencies, measured by UV–Vis spectrophotometer at 251 nm, were 3.74 mg/g for CMC, 3.67 mg/g for m-CMC and 10.62 mg/g for QCMC, respectively at 24 h loading period (no more drugs was loaded after longer loading times). According to the results obtained from UV–Vis spectrophotometer, the drug loading capacity of CMC particles was increased by chemical modification. The main reason of this increase was due to the electrostatic interactions between the newly formed functional groups on CMC and the drug. Drug release experiments were carried out in PBS, (pH = 7.4 prepared by using 0.140 M NaCl, 2.68 × 10^{-3} M KCl, 0.01 M Na_2HPO_4, and 1.76 × 10^{-3} M KH_2PO_4 according to the very well known recipe) at room temperature. The drug loaded particles were placed in PBS at room temperature and samples were taken in particular time intervals and UV–Vis spectrophotometer measurements were done and the released amounts were determined from a calibration curve. The results were graphed as amount of released drug against time. Although the same approximate amount of drug was loaded to CMC and m-CMC particles, CMC was released 21% of the loaded drug while m-CMC released 44% of the loaded drug when they were in equilibrium (Fig. 6(b)). The doubled amount of drug release can be attributed to the existence of Fe_3O_4 particles in CMC composites hindering the retention of drug by effecting the interaction of the drugs and CMC functional groups.

During the release study of the modified CMC particles, medium was changed with freshly prepared PBS as the system was reached in equilibrium in solution and drug content of CMC. Comparing the release results of QCMC with CMC particles, it was observed that while CMC particles were releasing 0.8 mg/g Ac, QCMC particles released 2.4 mg/g Ac a 3-fold increase in the released amounts with longer release times as shown in Fig. 6(c). This can be attributed to the electrostatic nature of the interaction between the positively charged CMC particles and negatively charged drug molecules. This interaction can readily be effected in the existence of other salts such as the ones used in preparation of PBS. Upon the change in medium with freshly prepared PBS at 175th min and 235th min, it was observed that the release was continuing in a similar trend as depicted in the inset of Fig. 6(c). The system reached in equilibrium at 535th min and QCMC particles released 3.61 mg/g Ac in total exhibited in Fig. 6(c). Therefore, it can be inferred that, this CMC particle can be modified chemically to introduce various functional groups for different formulation of drugs.

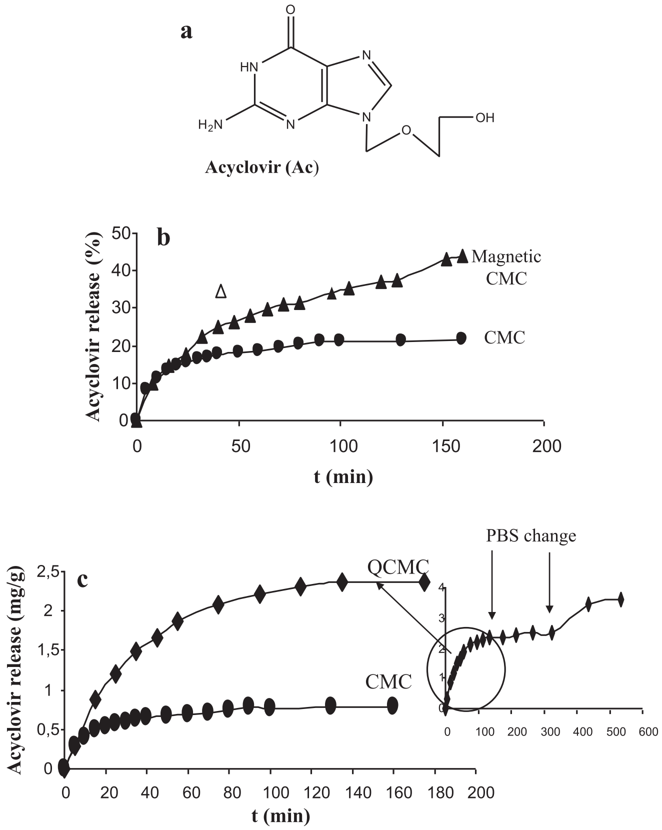

Fig. 6. (a) Chemical structure of Ac, (b) in vitro percent release of acyclovir from CMC particles and magnetic CMC particles in PBS (pH 7.4), (c) in vitro release of acyclovir from CMC particles and QCMC particles in PBS (pH 7.4).

To confirm that the particles can be separated to different size distributions by simple centrifugation three rational rate was chosen: 1000 rpm, 4000 rpm, 10,000 rpm. Since very little amount of particles obtained at 10,000 rpm centrifugation we employed particles that are obtained at 1000 rpm and 4000 rpm centrifugation. And to substantiate that more drug can be loaded to these particles, the drugs were loaded by repetitive loading processes ascribed above (3 times, 8 h loading times from 400 ppm 140 ml Ac solution). The total loading amounts were determined from UV–Vis spectrophotometer and found as 11.935 mg/g and 13.373 mg/g, for CMC and m-CMC, respectively that were obtained at 1000 rpm centrifugation. When smaller particles were used (4000 rpm) the amount of drug loading is more than that for bigger particles that was 15.575 mg/g. As the particle size decreased, the surface area was increased; therefore, this result is conceivable. Fig. 7(a) illustrates the release profile of particles with different sizes loaded with Ac at the same conditions. As can be seen from the figure, the smaller particle shown as (2) released more than twofold drug (6.83 mg Ac) than bigger sized particles shown as (1). Almost 44% of the loaded drug was released in about 5 h for smaller particle and 25% for bigger particles. As a proof of concept, this drug

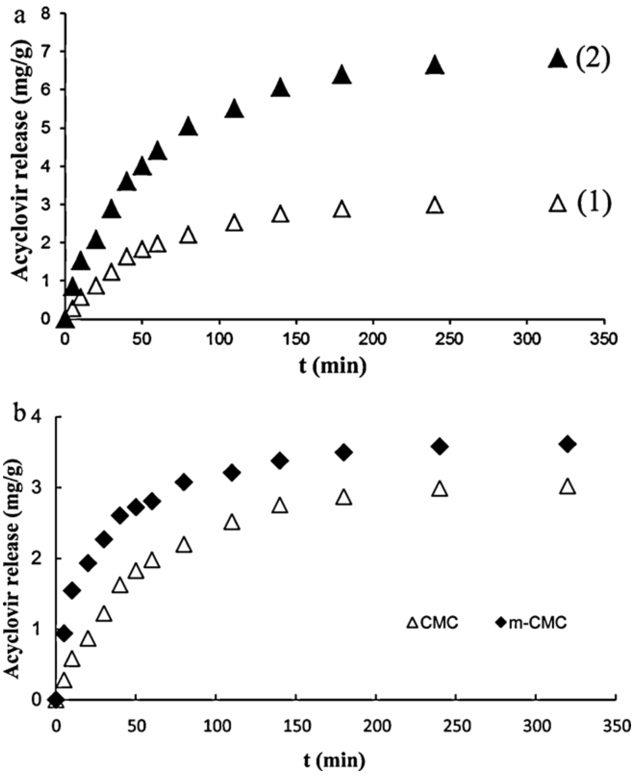

Fig. 7. (a) In vitro release profile of acyclovir from CMC particles centrifuged at 1000 rpm (1) and 4000 rpm (2), and (b) release profile of CMC and m-CMC particles centrifuged at 1000 rpm.

can also be loaded more into m-CMC particles, we compared the release profile of m-CMC and CMC particles obtained at 1000 rpm centrifugation and their release profile is depicted in Fig. 7(b). As can be seen both particle system show very similar Ac release trend about 5 h m-CMC and CMC released 3.61 and 3.03 mg/g particles. As expected the magnetic composite release slightly more than the bare CMC, same behavior was also observed with the particle before separation by centrifugation. It is also expected that after chemical modification (QCMC), the drug loading capacity can be improved drastically. Therefore, these kinds of materials have great potential in control and targeted drug delivery systems.

4. Conclusion

Carboxymethyl cellulose particles were synthesized successfully with high efficiency in a single step with reverse micelle microemulsion polymerization using divinyl sulfone as crosslinking agent. The synthesized polymeric particles have naturally negatively charged, and have a wide range of size distribution. It was demonstrated that this natural, biocompatible and biodegradable CMC particles can be used as drug delivery system. It was further confirmed that CMC particles are versatile and can be made magnetic responsive for potential targetable ability and resourceful to generate new functional groups (positive charges in this research). These modified forms of CMC particles had similar Ac loading capacities but m-CMC particles had a higher release capacity. The loading capacity of the particles was increased by chemical modification and prolonged drug release time was accomplished. Also multi step drug loading as shown in this investigation can dramatically increase the loading and release efficiency. It was also proven with this investigation that, an abundant biocompatible polymeric particles derived from CMC could be very useful and be used in the controlled and targetable drug release systems and can have many other biomedical potential applications.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carbpol.2011.05.001.

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