PREPARATION AND CONTROLLED DRUG RELEASE OF SODIUM ALGINATE/MCC HYDROGEL BEADS

TING GUO[1], FANG WANG[1], KEYONG TANG[1], MIHAELA VIOLETA GHICA[2]

[1] *College of Materials Science & Engineering, Zhengzhou University, Zhengzhou 450052, China, keyongtang@zzu.edu.cn*

[2] *"Carol Davila" University of Medicine and Pharmacy, Faculty of Pharmacy, 6 Traian Vuia Str., 020956, Bucharest, Romania*

In order to enhance the drug entrapment efficiency and to improve the swelling behaviors of drug delivery system, sodium alginate (SA)/microcrystalline cellulose (MCC) hydrogel beads were prepared with metformin hydrochloride (MH) as model drug. The hydrogel beads were crosslinked in Ca^{2+}, and the effects of MCC content and the crosslinking time on the properties of the beads were investigated. The chemical structure and morphology of the hydrogel beads were characterized by Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscope (SEM), respectively. The swelling and pH-sensitivity of the hydrogel beads were studied in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Results indicated that the MCC content of 20 wt% had the highest drug loading capacity and the lowest cumulative release percentage in 30 min in SIF. After prolonging the crosslinking time from 30min to 180min, cumulative release percentages of the beads with the MCC content of 60 wt % decreased by 30% in SIF.

Keywords: sodium alginate, microcrystalline cellulose, drug release.

INTRODUCTION

The ability of hydrogels to swell and regulate the release of encapsulated drugs by controlling cross-linking makes them attractive as materials in the controlled release (CR) of drugs (Graham and McNeil, 1984). Sodium alginate, widely used in food and pharmaceutical industries, is a water soluble salt of alginic acid, a naturally occurring non-toxic polysaccharide found in all species of brown algae (Rubio and Ghaly, 1994). Sodium alginate has a unique property of cross-linking in the presence of multivalent cations, such as calcium ions in aqueous media to form the 'egg box junctions' and insoluble calcium alginate (Smidsrod and Skjak, 1990). Calcium alginate beads can be produced by dropping a sodium alginate aqueous solution into a calcium chloride solution. Although this is a simple way of obtaining particulate drug carriers, drug loss and high permeability of pure SA hydrogel is considered a major limitation during drug-loaded beads preparation (Torre *et al.*, 1998). Hence, some researchers tried to circumvent this problem by preparing composite hydrogel beads such as SA/pectin (Liu and Krishnan, 1999), SA/chitosan (Anal and Stevens, 2005), SA/gelatin (Shinde and Nagarsenker, 2009) and even SA/PVA (Hua *et al.*, 2010).

In our study, we have tried to add a new member microcrystalline cellulose (MCC). It expected that the new kinds of hydrogel beads with improved structure and drug loading and release properties can be obtained by the combination of Gel, SA and MCC.

The aim of this work was to formulate a dual crosslinked SA/MCC matrix that effectively prolongs drug release, which is obtained by changing different proportion of MCC content. The structure and morphologies were characterized and the swelling properties, pH-sensitivity and their drug release behaviors were studied using metformin hydrochloride (MH) as the model drug.

MATERIALS AND METHODS

Materials

Sodium alginate (SA, a viscosity of 0.035Pa·s in 2% aqueous solution at 25°C) was from Paini Chemical Reagent Factory (Henan Province, China). Calcium chloride was purchased from Kermel Chemical Co. Ltd. (Tianjin, China). Microcrystalline cellulose was from Qufu Tianli Medical supplements Co. Ltd. (Shandong, China). Metformin hydrochloride was from Accela ChemBio Co. Ltd. (Shanghai, China). The simulated gastric fluid (SGF, pH 1.2) composed of 0.085M HCl, the simulated intestinal fluid (SIF, pH 7.4) composed of 0.05M potassium phosphate and 0.0395M sodium hydroxide. All the reagents used in this study were of analytical grade and used as received.

Preparation of SA/MCC Beads

Drug-loaded SA/MCC beads were prepared by droplet extrusion/precipitation of a sodium alginate/MCC aqueous mixture solution with metformin hydrochloride. The influence of ratios of alginate to MCC the drug loaded beads SM-0, SM-20, SM-40, SM-60 and SM-80 (0 wt.%, 20 wt.%, 40 wt.%, 60 wt.% and 80 wt.% of MCC, respectively) was investigated. The mixture was added into a gently stirred (100 rpm) 2.0% (w/v) calcium chloride aqueous using a syringe with the form of droplets, and the stirring was kept for additional 30min. After that, SM-20 and SM-60 were chosen to prolong the crosslinking time to 3hours and named SM-20-3h and SM-60-3h, respectively. The crosslinked spherical and homogeneous SA/MCC beads were obtained, and washed with distilled water three times. The resultant beads were dried at 45^{o}C for 9h.

Characterization

FTIR spectra were obtained at room temperature using a Nicolet Impacta 400 spectrometer (Nicolet iS10, USA) in the range of 4000-400cm-1 using KBr pellets. Surface morphology of the dried beads was characterized before release testing, samples of the beads were sputter coated with gold in a vacuum evaporator, and photographed using a scanning electron microscope (JSM-7500F, Japan) using an accelerating voltage of 20 kV.

Swelling Studies

Two aqueous media were used in swelling and drug releasing measurement: HCl buffer solution (SGF, pH1.2) and phosphate buffer solutions (SIF, pH7.4). Weighted dry beads were placed at 37.0±0.5˚C in conical flasks containing 200mL of buffer solution and magnetically stirred at 50 rpm. Swelling ratio was determined by measuring periodically the weight of swollen beads after wiping off excess of liquid with a filter paper. The weight change of the beads with respect to time was determined as follows:

$$\text{Swelling ratio}(\%) = \left(\frac{W_t - W_0}{W_0} \right) \times 100 \quad (1)$$

where W_t is the weight of the beads at time t; W_0 is the initial weight of beads.

In vitro Drug Release Profiles

The in vitro drug release tests were carried out using the magnetic mixer, the rotor was rotated at 50 rpm and 37.0±0.5˚C. The dissolution media used were PBS buffer at pH 7.4 and HCl buffer at pH 1.2. Weighted beads added to 200 mL dissolution medium. Samples (5 mL) were collected and replaced with the same fresh medium at various time intervals. The amount of drug released was analyzed spectrophotometrically at 230nm (UV-2550, Shimadzu, Japan). The UV standard absorbance curve for metformin hydrochloride was established in different buffer, and the UV absorbance obeyed the Beer's law in the concentration range from 1.2×10^{-5}-6×10^{-5}mol/L.

RESULTS AND DISCUSSION

Fig. 1 shows the wet and dried drug-loaded SA/MCC beads, generally, the beads are perfectly spherical and have a smooth surface, with a meas diameter of approximately 3.0 mm before oven drying. As expected, increasing of the MCC content leads to shape change of beads due to the viscosity increase of SA/MCC suspension and its filling effect. During oven drying, the initial spherical and oval shapes are lost and the particle shape changes significantly with MCC encapsulation. In addition, the beads change from transparent to white and the diameter decreases as the MCC content increasing.

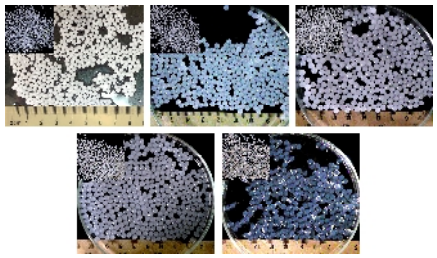

Figure 1. Photographs of wet and dry (upper left corner) with different proportions of SA/MCC drug-loading beads: (a) SM-80, (b) SM-60, (c) SM-40, (d) SM-20 and (e) SM-0

Fig. 2 shows the SEM images of sample SM-60 and SM-0 beads after dried by oven at 60^0C for 6h. The inclusion of MCC in the matrix creates beads with a rough surface and denser morphology (Fig. 2a, b). Fig. 2d reveals cracks caused by partial collapsing of the polymer network during dehydration. The results indicate that the addition of MCC caused the decrease of water evaporation from the beads during the drying period, then the collapse of polymers are less severe.

FTIR spectra of crosslinked SA/MCC beads and MCC were analyzed (Fig. 3). FTIR spectrum of beads showed the bands around 3412, 1636 and 1431 cm^{-1}, which was due to the stretching of −OH, asymmetric and symmetric stretching of -COO-. Compared with MCC, the absorption band of SM-60 around 3412 cm^{-1} shifted to a higher wavenumber at 3437 cm^{-1}, suggesting a possible break of hydrogen bonding intermolecular and intramolecular after the crosslinking. 1151 cm^{-1} was the asymmetric stretching of C-O-C from MCC. In order to recognize the possible effect of crosslinking scheme on drug release rate, a swelling study was conducted in advance of in vitro drug release study. Plots of dynamic swelling of beads in SGF (pH 1.2) and SIF (pH 7.4) buffer are given in Fig. 4.

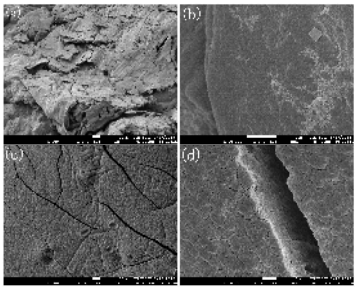

Figure 2. SEM micrographs of SM-60 (a, b) and SM-0 (c, d)

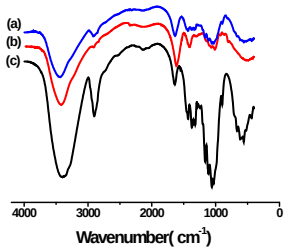

Figure 3. FTIR spectra of (a) SM-60, (b) SM-0 and (c) MCC

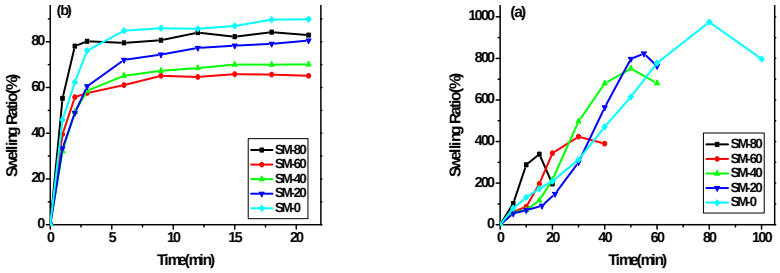

Figure 4. Swelling Ratio of dried beads made by different proportions MCC in SGF (a) and in SIF (b)

In the acidic environment of SGF, the SA/MCC beads began to swell immediately and reached the swelling equilibrium in 10min. As the MCC amount increased, the maximum swelling ratio at equilibrium decreased and then had a rise. It is obvious that in the neutral environment, maximum swelling time for beads was ranged from 15min and 80min, and the swelling ratio at equilibrium was 340% and 975%, respectively. The SA/MCC beads recovered their initial production spherical shape, and start to erode. At the neutral pH values, the affinity of phosphate present in PBS to calcium is higher than that of SA, and results in the breakage of Ca-SA beads. Besides this chelating action of the phosphate ions, the dissolving out of MCC made the phosphate ions infiltrated into the beads more quickly and improved the chelating action.

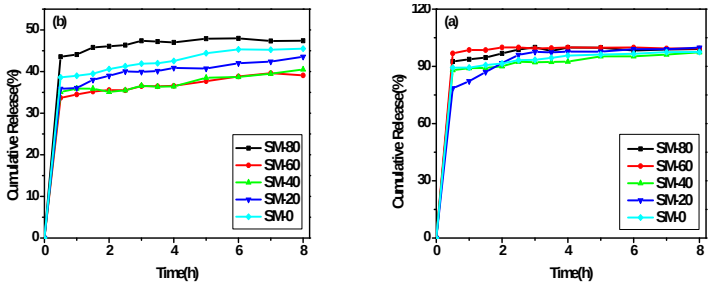

Figure 5. Release profiles of drug-loaded hydrogel beads of different proportions MCC in SGF (a) and in SIF (b)

Swelling behaviour of beads indicates the speed and easiness of a liquid to penetrate the alginate/MCC matrix, as a necessary step for drug release, whereas release tests show the evolution of bead structure during drug release. To study the release profiles of entrapped MH, dried test samples were immersed in SGF (pH 1.2) and SIF (pH 7.4) for 8h at 37^0C, respectively. In both buffer solutions, SM-80 drug release is rapid and most dissolution is attained within 3h. The MH adhered on the surface of the beads began to be dissolved and diffused into the buffer at the initially stage and showed quite brust release. Associated with the swelling behavior, MH total release from SM-60 was 40% in 8h, which was much lower than other formations (Fig. 5a). Under neutral conditions, 100% of MH was released in 8h. Meanwhile, SM-20 present a more stable and prolonged release profile, but as the MCC content continue to increase, the cumulative release began to be enhanced.

The comparison of Fig. 5 (a) and (b) showed that the release properties were associated with the swelling behavior of the beads and the beads present significant pH-sensitivity. MCC interpenetrated in the internal network and filled in the fracture and pore, meanwhile it had a certain effect with the drug adsorption which can slow down the drug release. The drug releasing process is further enhanced by the presence of phosphate ion, which acts as a calcium sequestrant. So the addition of MCC could show a sustained drug release at a certain extent.

With the purpose of improving the stable of the beads to control the drug release in PBS, the influence of crosslinking time was studied. After prolonging the crosslinking time, the swelling ratio at equilibrium decreased in both beads, and the swelling rate increased (Fig. 6). In SIF, increasing the crosslinking time reduced the swelling ratio at equilibrium and swelling rate for SM-60. The swelling ratio at equilibrium of SM-20 crosslinked for 3 hours is higher than for 0.5 hours.

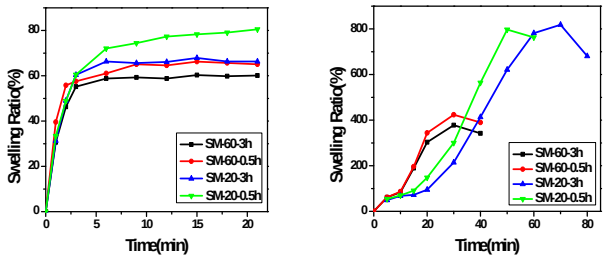

Figure 6. Swelling Ratio of dried beads made by different crosslinking time in SGF (a) and in SIF (b)

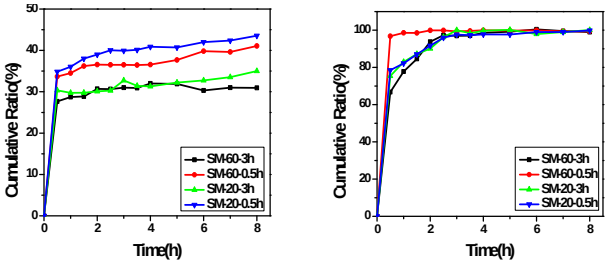

Figure 7. Release profiles of drug-loaded hydrogel beads of different crosslinking time in SGF (a) and in SIF (b)

In acidic medium, the beads presented a more stable network and was improved the release profile after extented the crosslinking time to 3h in Fig. 7. But in SIF, crosslinking time had no significant effect on SM-20. For SM-60, after prolong the crosslinking time, the cumulative release decreased from 97% to 66% in first half an hour and had obviously sustained release. MCC in the matrix absorbed water and swelled, preventing the further seeping of dissolution medium and thus helped to control the release of MH. But as the content increased, it leading to an easier water and phosphate ions (in SIF) permeation and swelling and, consequently, to faster drug release compared to the medium.

CONCLUSIONS

SA/MCC beads were successfully cross-linked by Ca^{2+} and used in the controlled release of metformin hydrochloride. All the materials used were environmentally friendly and the method developed was simple, fast and reproducible. A remarkable delay in the release of MH was observed for the beads with the MCC content of 20 wt% which had the lowest cumulative release percentage in first 30min in SIF and release slowly for 3h, but it had no significant effect on the swelling and release after prolong the crosslinking time for 3 hours. And SM-60 crosslinked for 3h presented obviously sustained release. Swelling and in vitro releasing behaviors demonstrate the formation of different kinds of SA/MCC matrix, it was observed that the release of MH was much higher in SIF compared to SGF, indicating that all the beads obtained were pH-sensitive and can be used as a release system for intestine specific drug delivery.

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