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Synthesis and characterization of superabsorbent hydrogels based on carboxymethyl cellulose and agar: Agar for smart swelling and controllable delivery

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Abstract
The current study described a thorough analysis of the adsorption characteristics of a hydrogel that was chemically connected and built on agar and carboxymethyl cellulose (CMC). With regard to swelling %, the Agar-Agar/ECH/CMC hydrogel was created under ideal conditions. In order to achieve the highest percentage of swelling, different response parameters were changed. The structure and morphology of the hydrogels were characterized by FT-IR spectroscope, thermogravimetric analysis and scanning electron microscope. The results revealed that the CMC contributed to the enhanced size of pore, whereas Agar-Agar as a strong backbone in the hydrogel to support it for keeping its appearance. Their equilibrium swelling ratio in distilled water and different physiological fluids were evaluated, indicating the maximum swelling ratio in water reached an exciting level of 1000 as the hydrogels still keeping a steady appearance. Moreover, the hydrogels exhibited smart swelling and shrinking in NaCl or CaCl2 aqueous solution, as well as the release behavior of bovine serum albumin (BSA) that could be controlled by changing CMC content. The Agar-Agar -based hydrogels are promising for the applications in the biomaterials area.

Keywords: Synthesis, characterization, superabsorbent hydrogels based, carboxymethyl cellulose

1. Introduction
Superabsorbent hydrogels are three-dimensional cross- linked hydrophilic, linear or branched polymers with the ability to absorb large quantities of water, saline or physio- logical solutions compared with general absorbing materi- als [1, 2]. Because of their excellent hydrophilic properties, high swelling ratio, and biocompatibility, hydrogels have been widely used in agriculture [3], biomedical area as anti- bacterial materials [4], tissue engineering [5], and biosensors [6,7], and sorbents for the removal of heavy metals [8] and drug delivery [9,10]. Usually, most hydrogels were prepared from synthetic polymers by radical copolymerization [11], frontal copolymerization [12, 13], graft copolymerization [14–16], crosslinking [17–22], and ionizing radiation [23]. It is worth noting that natural polymers have better biocompatibility and less latent toxic effect than most synthetic polymer hydrogels [24,25], so pure natural polymer hydrogels would be more suitable for biomaterials [26, 27].
Agar-Agar and sodium carboxymethylcellulose (CMC) are biocompatible and biodegradable, so they are often used in the biomedical field. Recently, Agar-Agar -based superabsorbent hydrogels prepared by using radiation induced crosslinking [28, 29] and chemical cross-linking [30, 31] have been investigated. Ibrahim et al. have synthesized cross-linked superabsorbent carboxymethylcellulose/acrylamide hydrogel through electron-beam irradiation, which can enhance the water retention of soil [3]. Biodegradable superabsorbent hydrogels have been prepared through etherifying of the Agar-Agar with succinic anhydride, which can absorb an amount of water of about 400 times of its dry weight [32]. So far, a considerable attention has centered on the applica- tion of superabsorbent hydrogels which possess high adsorbent capability, biocompatibility and biodegradability. Sannino et al. have reported that a superabsorbent hydrogel can be applied to body water elimination in the treatment of edemas [33]. The hydrogels have also been fabricated for a potential biomedical application as ‘‘barrier substances” to prevent post-surgical tissue adhesion [34]. However, the Agar-Agar -based superabsorbent hydrogels directly prepared from cellulose solution have been scarcely report, because of the insolubility of Agar-Agar in normal aqueous solution

due to its strong intermolecular hydrogen bonding. The aim of this paper was to prepare Agar-Agar/carboxymethyl cellulose (CMC) hydrogels in NaOH/urea aqueous system, by using epichlorohydrin as crosslinker. We attempted to introduce Agar-Agar as a backbone into the hydrogel for keeping its appearance when it absorbed large amounts of water. Moreover, CMC was used as hydrophilic filler in the hydrogel network to increase the absorbing of water. The structure and properties of the superabsorbent materials were evaluated. First, the intermolecular interaction and morphological change of the hydrogels were characterized by Fourier trans- form infrared (FT-IR) spectroscope, thermogravimetric analysis (TGA) and scanning electron microscope (SEM). Second, the swelling properties and salt-sensitivities were investigated by measuring the equilibrium swelling ratios and the swelling kinetics in different solutions. Third, the prolonged protein release behaviors of the hydrogels were also evaluated to afford important information for their application in the biomedical Field.

2. Materials and Methods

2.1 Materials

Carboxymethyl cellulose sodium salt, with medium viscosity (400–800 cps) and Agar- Agar was bought from HiMedia, India. Analytical NaOH and epichlorohydrin was procured from Sigma Aldrich, India. Deionised water was used throughout the project work.

2.2 Preparation of Agar-Agar/ECH/CMC hydrogel

The 3 wt% Agar-Agar solution was prepared as follows: 3 g CF-11 was dispersed into 97 g of 6 wt% NaOH/4 wt% urea/90 wt% water mixture with stirring for 5 min and then was stored under refrigeration (-20 °C) for 12 h. The frozen solid was thawed and stirred extensively at room temperature to obtain a transparent Agar-Agar solution. CMC was dissolved in the same solvent to obtain a 3 wt% polymer concentration. The CMC and Agar-Agar solutions were mixed with ratio of 5:5, 6:4, 7:3, 8:2 and 9:1 by weight, respectively. ECH was added to the mixture as crosslinker, stirred at 30 C for 2 h to obtain a homogeneous solution, and then kept at 60 C for 12 h to prepare gels. Gels were washed with water to obtain hydrogels.

2.3 Characterization

The hydrogel samples were ground into small particles and dried in vacuum at 50 C for 24 h. The dried samples were analyzed in KBr discs by FT-IR (Perkin Elmer Spectrum one, Wellesley, MA, USA). Thermo gravimetric analysis (TGA) was carried out on a Pyris TGA linked to a Pyris diamond TA Lab System (Perkin-Elmer Co., USA) at a heating rate of 10 °C min^{-1} from 40 to 500 °C under nitrogen atmospheres. Scanning electron microscope (SEM) was taken with a Hitachi X-650 microscope (Mountain View, CA, Japan). The hydrogels swollen to equilibrium in distilled water at 37 °C for 24 h were frozen in liquid nitrogen and snapped immediately, and then freeze-dried. The fracture surface (cross-section) of the hydrogel was sputtered with gold, and than observed and photographed.

2.4 Swelling measurements

The equilibrium swelling ratios (SR) of hydrogels were investigated in distilled water and various physiological fluids (D-glucose solution: 50 g D-glucose + 1000 mL distilled water; urea solution: 50 g urea + 1000 mL distilled water; physiological saline water: 9 g NaCl + 1000 mL distilled water; and synthetic urine: 8 g NaCl + 1 g MgSO4 + 20 g urea + 0.6 g CaCl2 + 1000 mL distilled water) as well as NaCl and CaCl2 solutions with different concentrations. The SR value was calculated as

$$SR = \frac{W_s}{W_d} \quad \text{....1}$$

where W_s is the weight of the wet hydrogel at swelling equilibrium at 37 °C, Wd is the weight of the hydrogel in the dry state. The shrinking rate in salt solution is important for smart hydrogels, and water retention is, usually, employed to measure their deswelling kinetics. Thus the shrinking rate in salt solution and water retention of the hydrogels were measured as follows. The hydrogels were immerged into 0.1 M NaCl and $CaCl_2$ aqueous solution, respectively. At each time intervals, the hydrogels were taken out and weighted after removing the excess solution on the surface. Water retention (WR) was calculated as

$$WR = \frac{(W_t - W_d)}{W_s} \times 100 \quad \text{...2}$$

where W_t is the weight of wet hydrogel at time t at 37 °C, W_d and $W_s$are same as Eq. (1). Water uptake (WU) is applied to characterize the reswelling kinetics of different hydrogel samples after dry. To measure WU, the dried gels were immerged again into distilled water at 37 °C. At each time intervals, the hydrogels were taken out and weighted after removing the excess solution on the surface. The WU value was calculated as

$$WU = \frac{(W_t - W_d)}{W_s} \times 100 \quad \text{...3}$$

where W_d, W_s and W_t are same as Eqs. (1) and (2).

2.5 *In vitro* proteins release

BSA was used as model protein to examine the smart release behavior of the superabsorbent hydrogels [35]. Drug-loading was carried out by reswelling the dried samples in BSA solution for 3 days. After the reswelling equilibrium was reached, the drug-loaded hydrogels were immersed in a phosphate buffer solution (PBS) solution (pH 7.4) at 37 °C to determine the release of the BSA. The BSA amount released in the solution was detected by ultraviolet–visible spectrophotometry (Shimadzu UV-160A). With each sampling, the solution was changed with fresh medium, while maintaining a constant total volume. All experiments were repeated three times. The cumulative protein release was calculated as follows:

$$\text{Cumulative release}(\%) = \frac{M_t}{M_0} \times 100 \quad \text{...4}$$

where M_0 is the amount of BSA preloaded into hydrogel and M is the amount of BSA released from the preloaded hydrogel in the solution at time t.

3. Results and Discussion

3.1 Appearance and structure of the hydrogels

Reaction conditions and the chemical composition of the Agar-Agar /CMC hydrogels are listed in Table 1. The hydrogel samples of GEL55, GEL64, GEL73, GEL82 and GEL91 having different ratio of CMC to Agar-Agar were prepared with ECH as a cross-linker. ECH has been widely used for the cross-linking of carbohydrates in polysaccharide chemistry [36, 37]. The proposed mechanism for cross-linking reaction of ECH with Agar-Agar and CMC in alkali solution is shown in Fig. 1. The hydroxyl groups of the Agar-Agar were cross-linked with hydroxyl groups of the CMC through nucleophilic attack of the alcoholate anion to form a monoethers of chloropropanediols and a new epoxide formed by chloride displacement. Subsequently, a reaction between the new epoxide and another alcoholate anion occurred, leading to the completion of the cross-linking. The photos of the GEL91 hydrogel at different states are shown in Fig. 2. The appearances of the hydrogels were different: the original hydrogel (a) was transparent and relatively small; the swollen hydrogel (b) was swollen in distilled water; dried hydrogel (c) with large shrinkage obtained after vacuum-drying the swollen hydrogel. Furthermore, the swollen gel was placed in 0.1 M NaCl solution to reach a new swelling equilibrium, and part of the water was extruded, leading to the obvious shrinking of the hydrogel (d). We did not obtain the hydrogel prepared from CMC only, because it was unable to hold a lot of water with stable appearance. This suggested that Agar-Agar acted as a strong backbone in the hydrogel for keeping its appearance, because the Agar-Agar chains are stiffness [42]. Fig. 3 shows the FT-IR spectra of Agar-Agar /CMC hydrogels. The broad absorption bands of the hydrogels at 3300-3500 cm^{-1} were assigned to stretching of the large number of hydroxyl groups on the backbone. The asymmetric and symmetric stretching vibration of CH2 was evidenced by the appearance of the absorption peaks at 2930 cm^{-1} and 2860 cm^{-1}. Compared with the Agar-Agar hydrogel without CMC (see Fig. 3a), the band observed at 1600 cm^{-1} and 1420 cm^{-1} in the Agar-Agar/CMC hydrogel can be attributed to COO^- stretching and bending respectively [38]. The results indicated that the carboxyl groups of CMC existed in the hydrogels.

Table 1: Reaction conditions and chemical composition of the Agar-Agar/ECH/CMC hydrogel

Sample code	CMC Solution (%)	Agar-Agar Solution	ECH (ml)	Time (Hr)	Temp (°C)
Gel 55	15	15	3	12	60
Gel 64	18	12	3	12	60
Gel 73	21	9	3	12	60
Gel 82	24	6	3	12	60
Gel 91	27	3	3	12	60

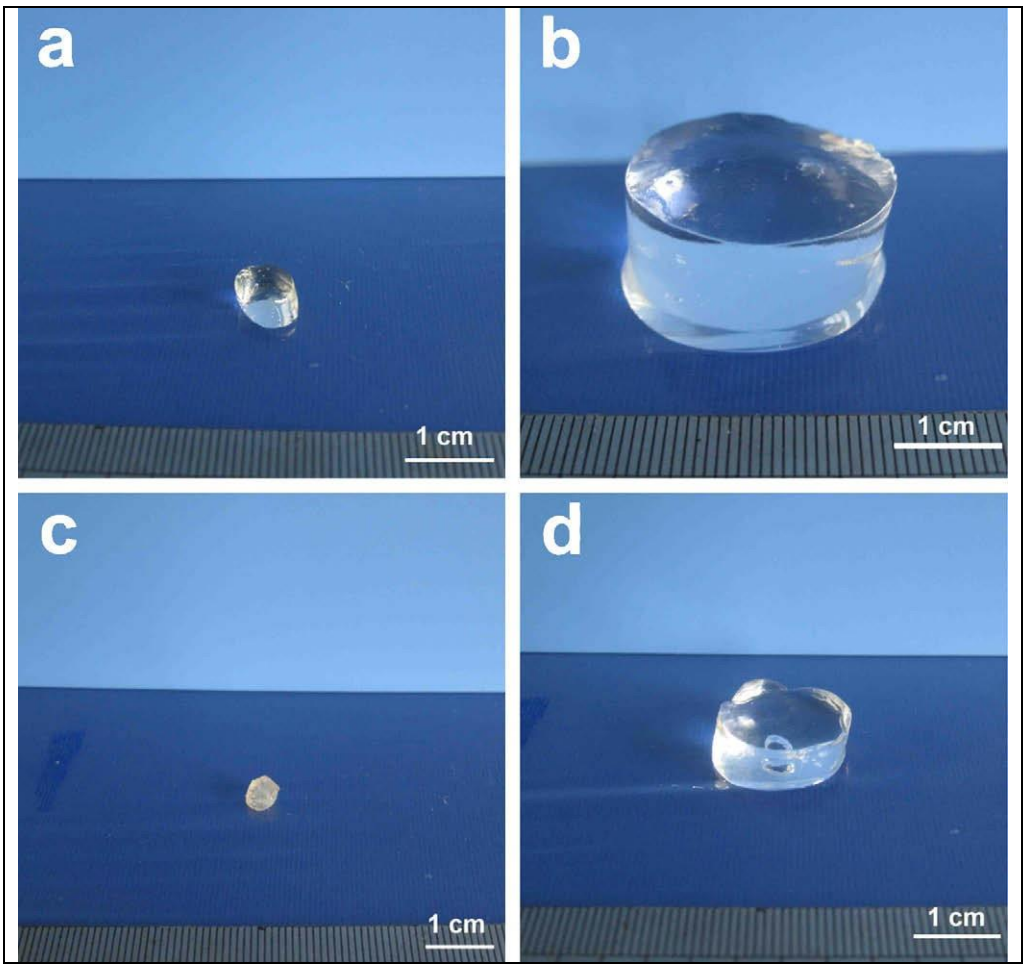

Fig 2: Photographs of GEL91: (a) original hydrogel, (b) swollen hydrogel, (c) dried hydrogel and (d) hydrogel after swelling in NaCl solution for a week.

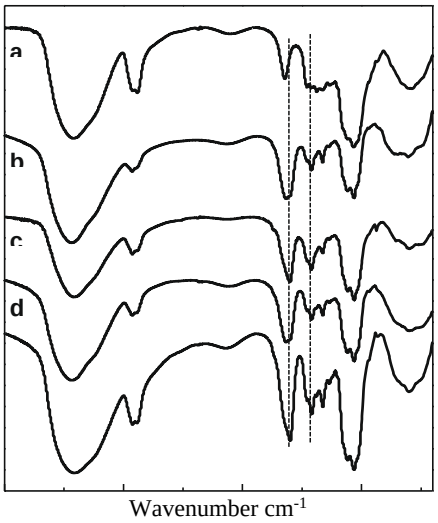

Fig 3: FT-IR spectra of Agar-Agar/CMC hydrogels: (a) Agar-Agar, (b) GEL64, (c) GEL73, (d) GEL82 and (e) GEL91.

3.2 Swelling properties of the hydrogels

The influence of the carboxymethylcellulose composition on the swelling ratio of Agar-Agar /CMC hydrogels in distilled water at 37 °C is shown in Fig. 4. The samples exhibited high equilibrium swelling ratio, indicating all of the samples were superabsorbent hydrogels. As expected, the equilibrium swelling ratio of the Agar-Agar /CMC hydrogels increased rapidly with an increase in the CMC contents. This confirmed further that highly hydrophilic carboxyl group of CMC could absorb a lot of water to enhance the space in the hydrogels. In the other hand, Agar-Agar /NaOH/urea aqueous solution could form irreversible gelation by heating [39], thus physical cross-linking in Agar-Agar also played an important role in the formation of hydogels. So, the entanglements of Agar-Agar chains through hydrogen bonds could occur easily in solutions of high Agar-Agar concentration, leading to the decrease of the equilibrium swelling ratio with an increase of Agar-Agar content. The maximum swelling ratio of the hydrogels was more than 1000, which was clearly higher than that prepared from Agar-Agar derivative [32]. It is important for biodegradable materials to have high swelling ratio for wide application in the biomedical. To evaluate the suitability of the Agar-Agar /CMC hydrogels as biomaterials, we studied their swelling ratios in different simulated biological solutions. Fig. 5 shows the effects of the D-glucose, urea, physical saline water and synthetic urine solutions on the swelling phenomena of the different hydrogels. All of the hydrogels exhibited the same shrinking behaviors in a given solution, as a result of the inhibition of the electrostatic effects caused by the charges of the carboxyl groups on the hydrogel backbones. Interestingly, the swelling ratio of hydrogels in D-glucose solution was as high as in distilled water, whereas it was considerably reduced in urea solution. However, the swelling ratios decreased quickly in physical saline water and in synthetic urine. These results indicated that the charge screening effect caused by cations (Na^+, K^+, Mg^{2+} and Ca^{2+}) in physical saline water and synthetic urine could induce a clear decline of anion-anion electrostatic repulsions, leading to a decrease of the osmotic pressure between hydrogel network and the external solution [40].

The effect of salt concentration on the swelling ratio of the Agar-Agar /CMC hydrogels is given in Fig. 6. In NaCl solution (Fig. 6a), the swelling ratio of hydrogels decreased with an increase of the ionic strength of the solution. The hydrogels with higher CMC contents exhibited more significant decline of swelling ratio with the increase of the NaCl concentration. In $CaCl_2$ aqueous solution, the swelling ratio decreased quickly because of the higher cationic charge of $CaCl_2$ in comparison with NaCl, in accord with the Donnan equilibrium theory. In this case, the distinction in the concentration of mobile ions between the hydrogel and solution was reduced. Therefore, the osmotic swelling pressure of mobile ions inside the hydrogel decreased, and the hydrogel collapsed [38].

Fig. 7 shows the shrinking kinetics of the Agar-Agar /CMC hydrogels in NaCl aqueous solution at 37 °C. All of the swollen hydrogels tended to shrink and lose water once transferred into NaCl solution. However, the water retention of the hydrogels decreased from 53% for GEL55 to 28% for GEL91 after 3 h with an increase of CMC content, indicating that screening effect became more significant in the hydrogels. Thus, a faster shrinkage of the hydrogel occurred in the NaCl solution. In view of the above results, the hydrogels possessed smart behaviors of swelling and shrinking in physical saline water, which will be very important for applications in biomaterials.

Fig. 8 displays the reswelling behaviors of the dried Agar-Agar /CMC hydrogels in distilled water at 37 °C. The reswelling capabilities of the hydrogels decreased with the increasing CMC content. The water uptake of dried GEL55 reached 91%, whereas that of dried GEL91 exhibited a low value of 19%. These results indicated that it was more difficult for the higher swelling ratio samples to reach their initial swollen state. In this study, strong hydrogen bonding interactions between the COO^- groups of CMC and the hydroxyl groups of Agar-Agar occurred during the desiccation process, greatly reducing the relaxation and expansion of the molecular chains. Therefore, the water uptakes of the hydrogels decreased with an increase of CMC content in the hydrogels from GEL55 to GEL91.

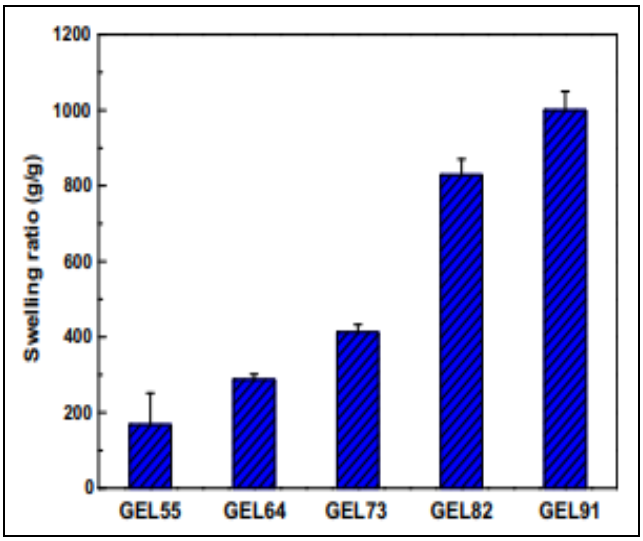

Fig 4: Equilibrium swelling ratio of the cellulose/CMC hydrogels after immersing in distilled water for a week, as a function of the composition of CMC and cellulose at 25 °C.

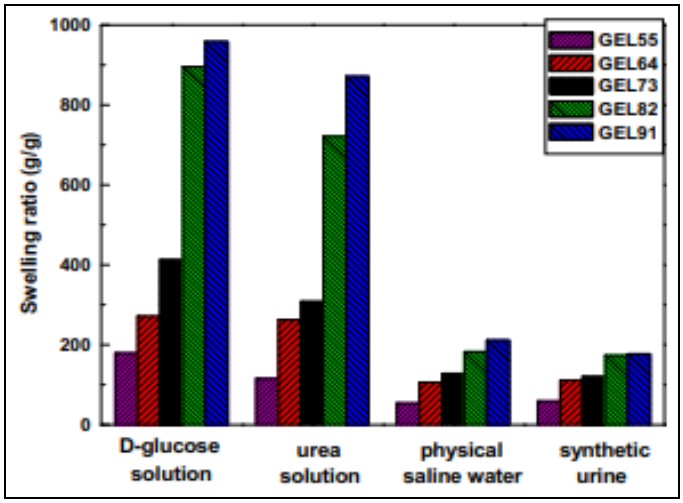

Fig 5: Effects of simulated biological solutions on swelling ratio of the cellulose/CMC hydrogels at 37 °C

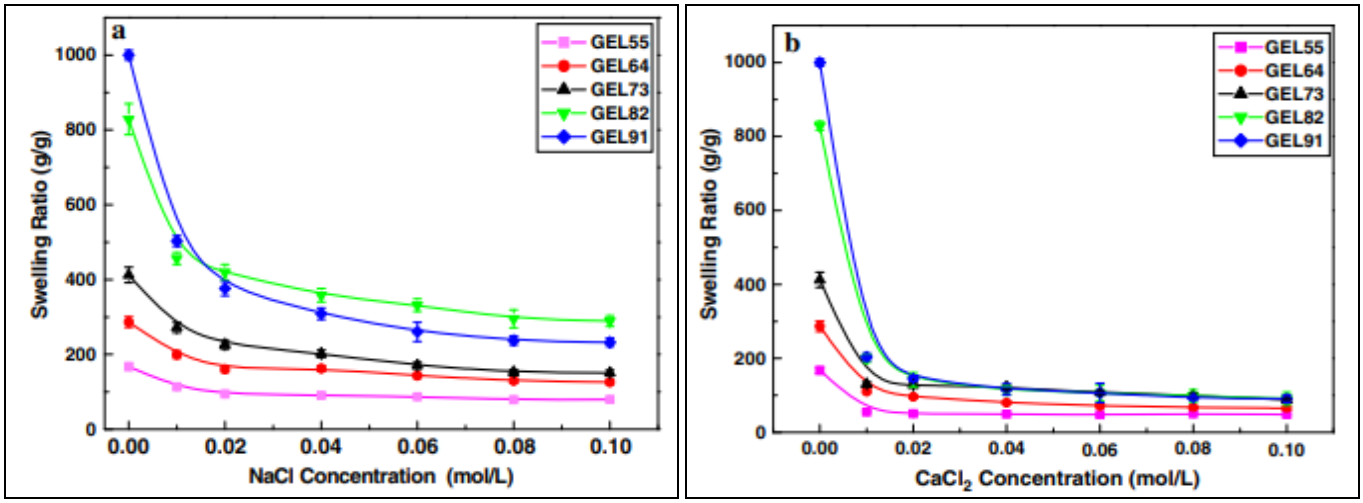

Fig 6: Effects of inorganic salt concentration on swelling ratio of the cellulose/CMC hydrogels: (a) NaCl, (b) $CaCl_2$

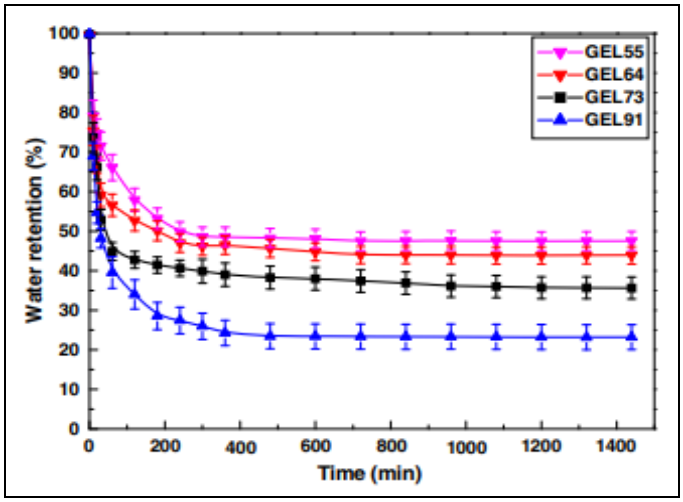

Fig 7: Deswelling kinetics of Agar-Agar/CMC hydrogels in 0.1 M NaCl solution at 37 °C

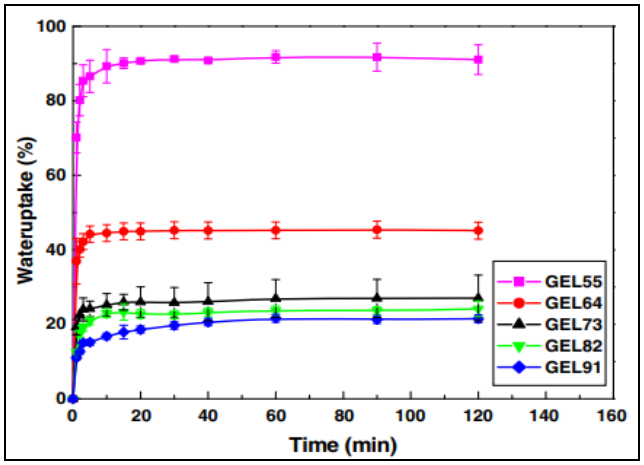

Fig 8: Reswelling kinetic of the cellulose/CMC hydrogels in distilled water at 37 °C

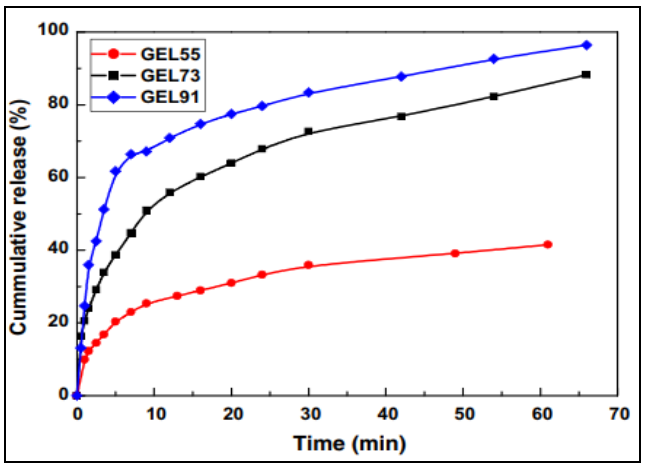

Fig 9: *In vitro* percent cumulative release of BSA from GEL55, GEL73 and GEL91 in PBS (pH 7.4) at 37 °C

3.3 Release behavior of bovine serum albumin

The *In vitro* release profiles of BSA from GEL91, GEL73 and GEL55 in a phosphate buffered solution (PBS pH 7.4) are shown in Fig. 9. There was a typical biphasic release pattern, namely a burst release followed by a slower sustained release. Initially, fast release of BSA was observed, especially in GEL91 in which more than 70% of BSA was released within the first 10 h, owing to the surface loaded BSA in hydrogel. The cumulative release percents of GEL55 and GEL73 were less than that of GEL91 during the same period of time. This result indicated that bigger pores of GEL91 induced faster release of BSA. Beyond the BSA located near the surface was exhausted [41]. After 60 h, the cumulative releases of BSA in GEL91, GEL73 and GEL55 were 96.5%, 88.3% and 41.5%, respectively. The result clearly revealed that these superabsorbent hydrogels could be a suitable polymeric carrier for protein drug release *In vitro*. 4.

4. Conclusions

Superabsorbent hydrogels were fabricated successfully from CMC and Agar-Agar in NaOH/urea aqueous solution by cross-linking with ECH. The superabsorbent mechanism could be described as that the stiff Agar-Agar molecules acted as the strong backbone of the network structure for keeping appearance of the hydrogels including a lot of water, and the highly hydrophilic CMC contributed to the higher swelling ratio. The experimental results proved that the Agar-Agar /CMC hydrogels exhibited superabsorbent capacity and high equilibrium swelling ratio, which could be improved by changing the amount of CMC. The hydrogels were sensitive to inorganic salts aqueous solution, physical saline water and synthetic urine, showing smart swelling and shrinking behaviors. The hydrogels possessed release behavior of BSA, and the release time could be controlled by the content of CMC. Their smart swelling, superabsorbent and controlled release properties will be very important in biomaterials.

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