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ORIGINAL ARTICLE

# One-step synthesis of interpenetrating network hydrogels: Environment sensitivities and drug delivery properties

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**Abstract** A novel interpenetrating network hydrogel for drug controlled release, composed of modified poly(aspartic acid) (KPAsp) and carboxymethyl chitosan (CMCTS), was prepared in aqueous system. The surface morphology and composition of hydrogels were characterized by SEM and FTIR. The swelling properties of KPAsp, KPAsp/CMCTS semi-IPN and KPAsp/CMCTS IPN hydrogels were investigated and the swelling dynamics of the hydrogels was analyzed based on the Fickian equation. The pH, temperature and salt sensitivities of hydrogels were further studied, and the prepared hydrogels showed extremely sensitive properties to pH, temperature, the ionic salts kinds and concentration. The results of controlled drug release behaviors of the hydrogels revealed that the introduction of IPN observably improved the drug release properties of hydrogels, the release rate of drug from hydrogels can be controlled by the structure of the hydrogels and pH value of the external environment, a relative large amount of drug released was preferred under simulated intestinal fluid. These results illustrated high potential of the KPAsp/CMCTS IPN hydrogels for application as drug carriers.


## 1. Introduction

Due to their inherited abundant strong hydrophilic groups such as carboxyl and low cross linking three dimensional network structures, hydrogels are paid extensive attention as promising water swelling functional polymer materials (Mehr et al., 2009). They can absorb hundreds or thousands of times

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of deionized water than themselves, meanwhile maintaining their three-dimensional network structure in insoluble state (Juby et al., 2012). At present, most hydrogels are based on acrylic acids, such as acrylamide and poly(acrylic acid) (Ruiz-Rubio et al., 2014), chitosan–acrylic acid (Gyarmati et al., 2014), poly(acrylic acid), poly(4-vinylpyridine) (Ge and Wang, 2014) etc. They are inferior to salt tolerance and non biodegradable that greatly limits their applications. Recently, poly aspartic acids have been widely studied because they have excellent properties such good biocompatibility, biodegradability, being nontoxic and environmentally harmless, etc. (Li et al., 2014). Poly(aspartic acid) hydrogels appear interesting for their biological and pharmaceutical applications because of their protein like structure and thermo-, pH- sensitivities (Liu et al., 2010; Matsuyama et al., 1980). Nevertheless, pure poly aspartic acid still exists in a simple structure and has poor salt tolerance. Instead, carboxymethyl chitosan (CMCTS), a water-soluble derivative of chitosan, has admirable biocompatibility (Chen et al., 2002), excellent biodegradability, and high moisture retention capacity (Chen et al., 2004). In particular, CMCTS contains a large amount of hydroxyl which can improve the salt resistance of polymers.

Interpenetrating polymer networks i.e., IPN are capable of combining 2–3 polymers to form a cross link network. Many studies have proven that IPN can greatly enhance the compatibility among the components and in turn ameliorate the network structures. They include gelatin/alginate (Hu et al., 2015) natural rubber/cassava starch (Mandal and Ray, 2014), chitosan/acrylic copolymer (Vudjunga et al., 2014), salecan/poly (N,N-dimethylacry lamide-co-2-hydroxyethyl methacrylate) (Hu et al., 2014), and acrylamide and potato starch (Dragan and Apopei, 2013). Typical swelling equilibrium IPN hydrogel can undergo a volume change with the small changes of environmental factors, e.g., temperature, pH, and ionic strength (Ashraf et al., 2013; Batool et al., 2015; Li et al., 2007), which is called environment sensitivity. Take an example of pH sensitivity, as an important role of the human body, it has gained great attention for its potential applications in oral drug controlled release systems. Moreover, in previous preparation methods exist several problems such as complex, asymmetric distribution, low effectiveness, etc. In particular, there is seldom address of preparation in an aqueous system. In this study, a simple one-step method was adopted to synthesize modified poly (aspartic acid) and carboxymethyl chitosan interpenetrating network (KPAsp/CMCTS IPN) hydrogels in an aqueous system.

## 2. Materials and methods

The novel KPAsp/CMCTS hydroxyls with semi-INP and IPN structures were prepared. The swelling properties and salt, temperature and pH-sensitivities of KPAsp, KPAsp/CMCTS semi-IPN and KPAsp/CMCTS IPN hydrogels were investigated The cross-linking structure and swelling properties of KPAsp, KPAsp/CMCTS semi-IPN and KPAsp/CMCTS IPN hydrogels were proved by FTIR, SEM and tea-bag methods. Their sensitivity characteristics to pH, temperature and salts were also investigated. Furthermore, the drug release properties of the KPAsp, KPAsp/CMCTS semi-IPN and KPAsp/CMCTS IPN hydrogels have been studied.

N,N-dimethylformamide (DMF), Ethanol absolute were purchased from Tianjin Kemiou Chemical Regent Company, China. Glutaraldehyde, 3-aminpropyltriethoxysilane (KH-550), Sodium chloride (NaCl) and Sodium hydroxide (NaOH) were obtained from Tianjin Fengfan Technology Chemical Regent Company Ltd., China. Ferric trichloride and anhydrous calcium chloride were procured from Tianjin Damao Chemical Regent Company Ltd., China. All reagents were of analytical grade. CMCTS was provided by the Nanjing Chemical Industry. Polysuccinimide (PSI) was prepared in our laboratory (Rajapakse et al., 2005).

The novel hydrogels were prepared by KPAsp and CMCTS in aqueous solution. The KPAsp/CMCTS semi-IPN and IPN hydrogels were complied with the cross-linking reaction mechanism, as illustrated in Fig. 1.

1 g of PSI and 10 ml DMF were simultaneously put in a 100 ml beaker under magnetic stirring at 35 °C. After PSI was completely dissolved, an amount of 1.8 mol% of KH-550 (based on PSI) was added into the solution and maintained for 3 h. The alcohol washing procedure lasted three times. Subsequently the precipitate was separated by filtration and dried at 50 °C in a vacuum oven. The KH-550 grafted PSI was then obtained.

1 g KPSI was dispersed into 20 ml deionized water. Then NaOH with a concentration of 2 mol/l was dropwise added to execute the hydrolysis reaction till the pH value reaches 10. This procedure lasted about 4 h. The product was kept in a vacuum oven at 75 °C for further reaction for another 2 h. After that, the final product was separated by alcohol filtration, dried and milled at 50 °C. The KPAsp hydrogel was then obtained.

Similarly, 1 g of KPSI was dispersed into 20 ml deionized water. Then 24.5 ml aqueous solution of CMCTS (containing 0.6 g CMCTS) was poured into the KPSI solution with agitation and heated to 35 °C. Next, NaOH (with a concentration of 2 mol/l) was added drop-wise into the solution to maintain the pH at 10 for 4 h. Half an hour before hydrolysis reaction completed, the cross-linker, glutaraldehyde (4.2 mol% based on CMCTS) was added. The solution was put in a vacuum oven at 75 °C for further reaction for 2 h. Afterward, alcohol was added to the solution, the precipitate was separated by filtration and dried at 50 °C in a vacuum oven. Thereby the KPAsp/CMCTS IPN hydrogel was obtained. KPAsp/CMCTS semi-IPN hydrogel was also prepared in the same manner without the addition of glutaraldehyde.

FTIR spectra were recorded on a Shimadz-8400S FTIR instrument (Japan) in the range of 500–4000 $cm^{-1}$ with a resolution of 2 $cm^{-1}$. The vacuum-dried samples of KPAsp, semi-IPN, and IPN hydrogel were dispersed in potassium bromide (KBr) pellets.

The surface and morphologies of different hydrogels were examined using SEM (MIRA3, UK). Samples were sectioned into slices and mounted on aluminum stubs, using a double-sided adhesive tape. The samples were then directly visualized by SEM at an accelerating voltage of 10 kV after sputter-coating with an ultrathin layer of gold.

Thermogravimetry analysis (TGA) was carried out on a TGA-50 Shimadzu instrument (Japan), over a temperature range of 40–600 °C. The heating rate was 10 °C $min^{-1}$ and the nitrogen flow rate was 100 ml $min^{-1}$.