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Honeycomb structural composite polymer network of gelatin and functional cellulose ester for controlled release of omeprazole

Chen Zhuang, Chengmei Shi, Furong Tao*, Yuezhi Cui

Shandong Provincial Key Laboratory of Fine Chemicals, Qilu University of Technology, Jinan, 250353, PR China

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ABSTRACT

The functionalized cellulose ester MCN was firstly synthesized and used to cross-link gelatin by amidation between $-NH_2$ in gelatin and active ester groups in MCN to form a composite polymer network Gel-MCN, which was confirmed by Van Slyke method, FTIR, XRD and TGA-DTG spectra. The model drug omeprazole was loaded in Gel-MCN composites mainly by electrostatic interaction and hydrogen bonds, which were certified by FTIR, XRD and TGA-DSC. Thermal stability, anti-biodegradability, mechanical property and surface hydrophobicity of the composites with different cross-linking extents and drug loading were systematically investigated. SEM images demonstrated the honeycomb structural cells of cross-linked gelatin networks and this ensured drug entrapment. The drug release mechanism was dominated by a combined effect of diffusion and degradation, and the release rate decreased with cross-linking degree increased. The developed drug delivery system had profound significance in improving pesticide effect and bioavailability of drugs.

1. Introduction

Composite polymer network made of biodegradable materials can act as efficient drug delivery vehicles for controlled and targeted release, aiming to improve the therapeutic effects and also to reduce the side effects of the formulated drugs [1]. Over the past few decades, the use of natural polymers such as gelatin [2,3], starch [4,5], chitosan [6,7], cyclodextrin [8], cellulose and its derivatives etc. [9–11] as carriers in controlled drug delivery applications have been brought to the forefront because of their inherent biocompatibility, biodegradability and biosafety. These novel carriers offer several advantages over conventional dosage forms and modify the solubility, *in vivo* stability, pharmacokinetics and pharmacodynamics of drugs, especially systems composed of gelatin and cellulose, which are most easily available, nontoxic and actively reactive.

Gelatin, a natural protein derived from the hydrolysis of collagen under acidic or alkaline conditions, has a long history of safe usage in biomaterials, cosmetics as well as food products. Although mainly derived from animals, the digestive process confers gelatin very low antigenicity with the formation of harmless metabolic products upon degradation [12]. The good biological properties, such as high biocompatibility and biodegradability in the physiological environment, promotion of cellular proliferation and differentiation, acceleration of platelet clotting and low toxicity, grant its wide applications as different kinds of biomaterials, e.g. wound dressings, sponges, nanoparticles, microspheres, scaffolds and films etc. [13–18]. Indeed, as drug delivery carrier, gelatin has proven to be versatile due to its intrinsic features that enable the loading of charged biomolecules and the isoelectric point (pI) can be tailored to maximize drug loading efficiency depending on the electrostatic properties of the desired drug molecule. In addition, it is considered as GRAS (generally regarded as safe) material by the United States Food and Drug Administration (FDA) [19] and this guarantees its biosafety in pharmaceuticals application. However, the relatively weak thermal stability, poor mechanical properties and easily-degradable quality make the modification of gelatin by other materials urgent. Kevadiya et al. [20] reported intercalation of ciprofloxacin into montmorillonite and its reaction with gelatin that yielded three-dimensional composite hydrogel. The drug intercalation into the layered nanostructure silicate was through ion-exchange and the in vitro release behavior of ciprofloxacin was studied by HPLC. Li et al. [21] developed a co-delivery strategy to achieve the synergistic effect of a hydrophobic drug (camptothecin) and a hydrophilic drug (doxorubicin) by utilizing the unique structure of amphiphilic gelatin/camptothecin @calcium phosphate-doxorubicin nanoparticles as a carrier. Khan et al. [22] modified gelatin by cross-linking with genipin and

* Corresponding author.
E-mail address: frao2015@126.com (F. Tao).

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regulated the swelling extent of the obtained nanoparticles to control the release of cytarabine drug.

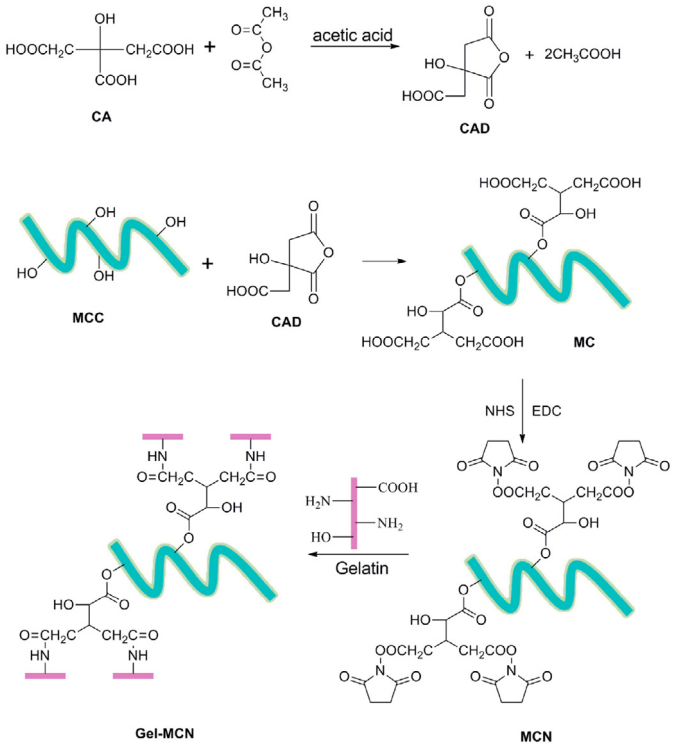
The linear polysaccharide molecule, microcrystalline cellulose (MCC), which comes from abundant renewable resources, assembles excellent properties such as biodegradability, nontoxicity and good compatibility with life entity. And these advantages over the materials referred above ensure its application as drug delivery system [23,24]. Besides, it is also widely used for perfecting gelatin to manufacture a new and novel biopolymer matrix with further outstanding performance. Ooi et al. [25] prepared a gelatin hydrogel reinforced by cellulose nanocrystals using glutaraldehyde as cross-linker with remarkable sensitivity toward changes in pH and studied drug loading efficiency and release profiles of theophylline. Rokhade et al. [26] successfully encapsulated ketorolac tromethamine into the semi-interpenetrating polymer network (IPN) microspheres of gelatin and sodium carboxymethyl cellulose with glutaraldehyde as cross-linker and investigated the drug release behavior. Raghavendra et al. [27] impregnated gelatin-cellulose fibers with aqueous based nanocurcumin for the first time and carried out the cumulative releasing studies of curcumin and nanocurcumin. As macromolecule active substances, cellulose is normally blended, mixed or in virtue of other cross-linkers like glutaraldehyde, whose toxicity is hard to eliminate to form composite network with gelatin. The chemical reaction between cellulose and gelatin is rarely reported. So the modification and functionalization of cellulose is critically needed for introducing highly reactive functional groups. Citric acid (CA) is usually used as food additives [28–30] while the extensive distribution in nature, special anticoagulation effect, participation in energy conversion and cycle of human body favor its application in medical fields, especially combined with gelatin and cellulose [31–33]. Its five-mem bered cyclic anhydride, citric acid anhydride (CAD) can be applied to functionalize cellulose according to Gil's group [34]. Omeprazole (opl), 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2- pyridinyl)methyl] sulphinyl]-1H-benzimidazole, is the first "proton pump inhibitors" widely used for the prophylaxis and treatment of gastro-duodenal ulcers [35–37]. It is a lipophilic drug and will be degraded unless it can be protected against acid conditions. So an efficient drug delivery system is necessary to improve the drug bioavailability, *in vivo* release characteristics and decrease its side effects.

In this paper, MCC was modified with CAD to get functionalized cellulose MCC-CAD (MC). Then MC was activated by N-hydroxysuccinimide (NHS) in the presence of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC) with a novel functional cellulose ester (MCN) synthesized to crosslink gelatin (Scheme 1). A novel honeycomb structural composite polymer network (Gel-MCN) was obtained by freeze drying technique. The structural and crystallinity properties, thermal stability, *in vitro* biodegradation studies, mechanical property and surface hydrophobicity of the polymeric matrix were investigated. Omeprazole, as a model drug, was selected to evaluate the potential of the composites to act as drug carriers and the *in vitro* drug release behavior under different cross-linking degree were also recorded.

2. Experimental

2.1. Materials

Gelatin (type A, obtained from pigskin, with an approximate molecular weight of 50,000 and isoelectric point at pH = 8 determined by fluorescence measurements) and omeprazole were obtained from Sinopharm Chemical Reagent Co., Ltd. MCC (extra pure, average particle size 90 μm), NHS (AR, 98%), EDC (AR, 99%) and citric acid (AR, 99%) were purchased from Energy Chemical



Scheme 1. The synthetic route of cross-linked gelatin with MCN.

Technology Co., Ltd (Shanghai). Glycerol (AR, 99%), DMF (AR, 99.5%), chloroform (AR, 99%), acetic acid (AR, 99%), acetic anhydride (AR, 98.5%) and other agents were obtained from Tianjin Fu Yu Fine Chemical Co., Ltd. All chemicals and reagents were used as received.

2.2. Preparation of MCN

2.2.1. Synthesis of citric acid anhydride (CAD)

CAD was synthesized by anhydrous citric acid (CA), acetic anhydride (AAD) with acetic acid (AA) as solvent according to Shi's method [38]. The reaction conditions were: reaction time 18 h, reaction temperature 37 °C, molar ratio of n (CA): n (AAD): n (AA) = 1:1.8:2. After reaction, the solvent was removed by vacuum distillation and the remains were washed with chloroform under stirring. The precipitate was vacuum filtered and rinsed with chloroform 2 ~ 3 times, subsequently dried in an oven at 60 °C. The yield was 84%. The prepared CAD was characterized by ^{1}H NMR spectrum (Bruker Advance 400 spectrometer) and FTIR spectrum (Nicolet NEXUS 470 FT-IR spectrometer).

2.2.2. Functionalization of MCC with CAD (MC)

MCC was functionalized by CAD according to Gil's group [34] with slight modification. 2 g MCC and 12 g CAD were suspended in 150 ml DMF, which were stirred and heated under reflux at 70 °C for 24 h. The materials were filtrated under reduced pressure, washed sequentially with DMF, distilled water, saturated $NaHCO_3$ solution, distilled water, and ethanol, and then dried under vacuum at 50 °C.

2.2.3. Synthesis of functional cellulose ester (MCN)

MCN was prepared by the method of our former study [39] with a bit improvement. Relevant quantity of MC, NHS, EDC was weighed by the ratio of 1:2:4 and dissolved in distilled water. After gently stirred for 1 h at 25 °C, the solid was vacuum filtered, washed with distilled water several times and dried under vacuum at 50 °C to get purified MCN. The MC and MCN obtained were characterized using FTIR spectrum, Elemental Analyzer (Vario EL