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Preparation of dual responsive low-molecular-weight hydrogel for long-lasting drug delivery

Ning Tao, Guotao Li, Miaochang Liu, Wenxia Gao*, Huayue Wu**

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325027, China

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ABSTRACT

A novel low-molecular-weight hydrogel (LMWG) was fabricated by oligopeptide and phenylboronic acid to obtain a smart molecular hydrogel with dual glucose and pH response for long-term drug delivery in this study. Dual glucose and pH responsiveness of the blank molecular hydrogel was first evaluated by on-line tracking the dynamics curves using UV spectroscopy. Model drugs of phenformin for antidiabetes and doxorubicin for anticancer were selected to evaluate the drug carry and glucose/pH responsive drug release of the molecular hydrogel. The results showed the drug-loaded LMWG had good sustaining and long-lasting drug delivery in physiological or pathological environment.

1. Introduction

Low-molecular-weight hydrogels (LMWGs), as the supramolecular hydrogels, have attracted considerable attention in recent years due to their super-sensitivity to external stimuli.[1,2] Since the solid like LMWGs were formed by the self-assembly of low-molecular-weight hydrogelators into three-dimensional fibril-net to entrap water molecules, the gel-sol transition could be easily achieved by changing the pH, temperature, light, ultrasound, or specific molecules.[3–5] These stimuli-responsive LMWGs exhibited specially potential applications in sensors and controlled drug delivery.[6,7] Molecular hydrogels were not only used as carriers for the delivery of both hydrophilic and hydrophobic drugs,[8,9] but also used as prodrugs,[10,11] for example the gels formed by the conjugate of Taxol and a short peptide derivative of anti-inflammatory,[12,13] by two complementary anti-cancer drugs of dexamethasone and Taxol,[14] or based on an antiepileptic drug carbamazepine to be the self-delivery system.[15] Though LMWGs usually show the capacity of sustaining or controlled release of drugs as drug carriers, the small molecular hydrogels currently reported could not be stable enough for a long-term in the release media for the damage of intermolecular hydrogen bonding from the water molecules, so the molecular hydrogels as a prodrug or drug carrier could not well achieve the long-lasting and controlled release in practice.[16,17] Long-term stable molecular hydrogels with the responsive release of drug to physiological or pathological environment are more favored.[18,19]

In our previous study, we obtained a molecular organogel based on phenylboronic acid exhibiting excellent and selective sensitivity to glucose and resisting the interference of other sugars (i.e., mannitol, galactose, lactose, maltose, sucrose, and fructose).[20] And the correlation of the molecular structure and glucose sensitivity was further illustrated to make the glucose sensitivity be controllable modulated.[21] Though these superior performance could be used for drug controlled release, all the previous findings were organic gels, not suitable for drug carrier. Therefore, in this study, we introduced appropriate number of hydrophilic and biocompatible glycine to successfully fabricate a novel molecular hydrogel basing on oligopeptide and phenylboronic acid. This molecular hydrogel was also a smart gel with dual glucose and pH response, and this hydrogel has the capability in sugar/pH detection and self-tuning controlled-release used in treating diabetes mellitus, anticancer, a worldwide health concern.[22,23] This molecular hydrogel was further investigated for long-term drug delivery, and model drugs of phenformin for antidiabetes and doxorubicin for

* Corresponding author.
** Corresponding author.
E-mail addresses: wenxiag@wzu.edu.cn (W. Gao), huayuewu@wzu.edu.cn (H. Wu).

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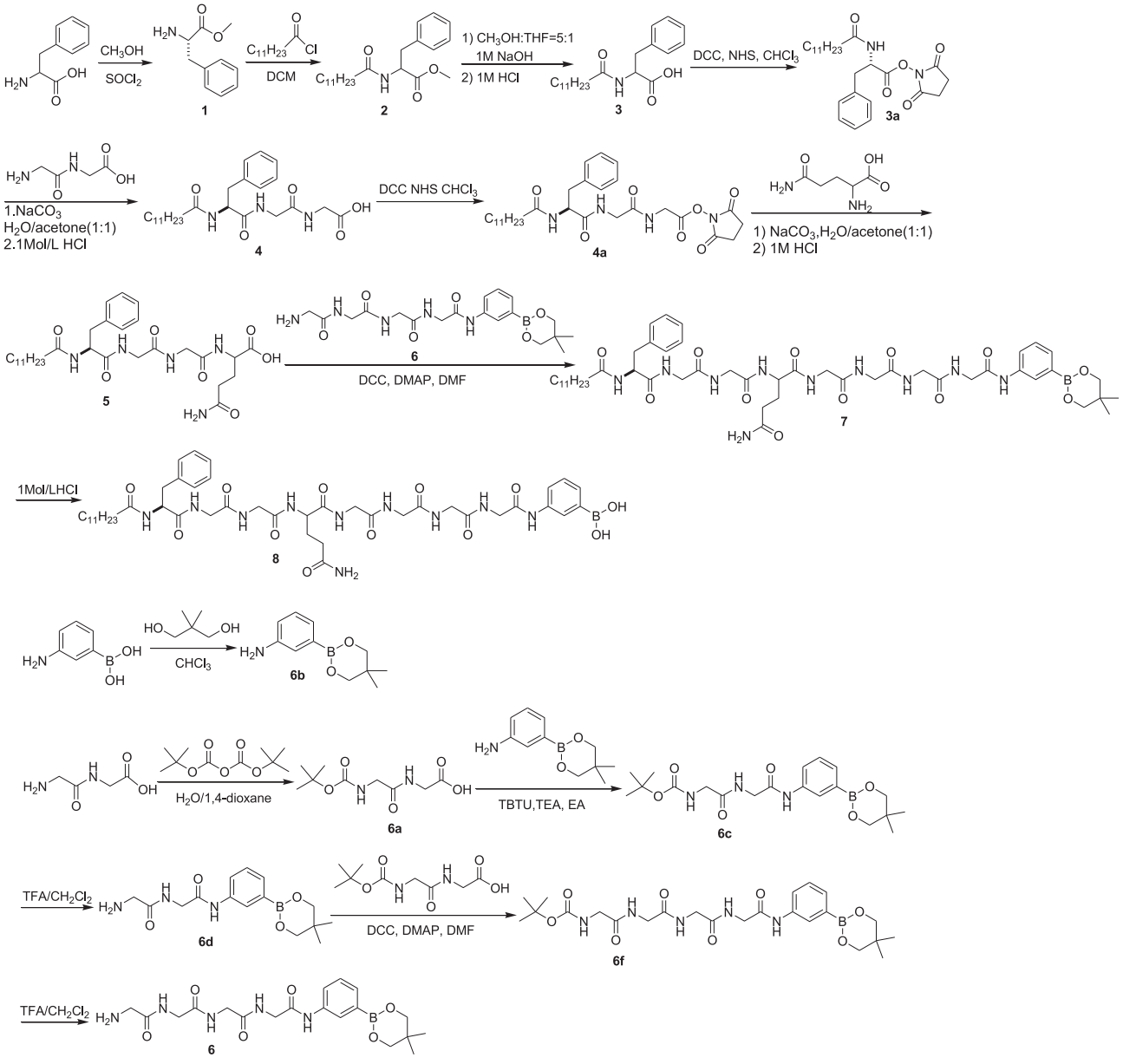
anticancer were selected to evaluate the drug carrier and delivery.

2. Results and discussion

The gelator (compound **10**) was synthesized by oligopeptide and phenylboronic acid to obtain dual glucose and pH response (Scheme 1). The oligopeptide made of natural amino acid of L-phenylalanine, glycylglycine and L-glutamine was used to regulate the hydrophilicity of gelator. And the alkyl chain of lauroyl chloride was involved to regulate the hydrophobicity of gelator. The phenylboronic acid group mainly acted as the glucose-sensitive moiety. The synthesized gelator had good gelation behavior in water with the critical gelation concentration of 3.0 mg/mL. Subtransparent gel was acquired from the transparent sol in phosphoric acid buffer solution (PBS) (pH = 7.4) (Fig. 1A). SEM image (Fig. 1B) of the xerogel indicated that the gel was consisted of nanofibers (20–100 nm wide), which assembled into a three-dimensional and compact nanofiber-net. The one dimensional structure of the fiber can also be observed by TEM (Fig. 1C). The drug-loaded gel was prepared by the cogelation of gelator and DOX·HCl in PBS 7.4 (pH = 7.4) (Fig. 1D), which showed three-dimensional porous structure (Fig. 1E). This structure was different from that of blank gel, which demonstrated the drug of DOX was involved in the formation of the gel through intermolecular interactions, and the intermolecular interactions would further affect the drug release, which was explained detailed later.

Further investigation of rheological properties of the gel was carried out. The frequency dependence of storage modulus (G′) of the gels with two concentrations were higher than their corresponding loss modulus (G″), it demonstrated that real gels were formed (Fig. 1F).[24,25] As for the gel with concentration of 3 mg/mL, the G′ was 4.99×10^2 Pa, the G′ increased greatly to 2.76×10^4 Pa as the concentration increasing to 10 mg/mL. The mechanical strength of this gel was concentration depended, when the gel was used as drug carrier, strength of the gel could be adjusted by choosing the appropriate concentration according to different usage.



Scheme 1. Synthesis of gelator.