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Three-dimensional printing of shape memory hydrogels with internal structure for drug delivery

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ABSTRACT

Hydrogels with shape memory behavior and internal structure have wide applications in fields ranging from tissue engineering and medical instruments to drug delivery; however, creating the hydrogels has proven to be extremely challenging. This study presents a three-dimensional (3D) printing technology to fabricate the shape memory hydrogels with internal structure (SMHs) by combining sodium alginate (alginate) and pluronic F127 diacrylate macromer (F127DA). SMHs were constituted by a dual network structure. One is a stable network which is formed by F127DA photo-crosslinking; the other one is a reversible network which is formed by Ca^{2+} cross-linked alginate. SMHs recovery ratio was 98.15% in 10 min after Ca^{2+} was removed in the Na_2CO_3 solution, and the elastic modulus remains essentially stable after the shape memory cycle. It showed that the drug releasing rate is more rapid compared with traditional drug-loaded hydrogels in in vitro experiments. The viability of 3T3 fibroblasts remained intact which revealed its excellent biocompatibility. Therefore, SMHs have a huge prospect for application in drug carriers and tissue engineering scaffold.

1. Introduction

Shape memory hydrogels are a class of gel that can restore its original form in the presence of external stimuli [1–3]. Lendlein reported a PCL-based shape memory polymer (SMPs) and demonstrated its potential in medical applications [4]. Since then more and more research focused on the development of SMPs biocompatible applications [5,6]. Willner et al. have developed DNA hydrogels with shape memory performance by regulating pH value [7,8]. Yakacki et al. have proposed a shape memory polymer for cardiovascular stent [9]. Shape-memory in drug controlled release devices was reported by Wischke et al. [10]. Drug release from the tablets depended on the surface area to volume ratio [11]. The internal structure of the hydrogel can change its surface area volume ratio to have a positive effect on drug controlled release [12]. The internal structure of the hydrogel is widely used in cell culture [13] and tissue engineering scaffolds [14,15] because it uses less material to provide space support for cell growth. For example, Erndt-Marino et al. reported a cell layer-electrospun mesh internal structure as coronary artery bypass grafts [16]. Lin et al. reported 3D printing polyrotaxane-based lattice cubes which are capable of converting the chemical energy input into mechanical work; it is also proved that the polymer without the internal structure cannot achieve this conversion effect [17]. So the shape memory hydrogel with internal structure has a huge potential value in the medical field. But there is still no effective way to control the internal structure of the shape memory hydrogels.

To address this issue, an attractive strategy would be the introduction of a 3D printing technique applied to the manufacturing process of shape memory hydrogels. 3D printing is recognized as a promising technology since it was developed by Charles Hull in the early 1980s [18]. Nowadays, the development of computer-aided design and image processing enable 3D printing to reconstruct an accurate physical model [19–21]. 3D printing technology used in the manufacture of SMPs is also gradually reported [17]. A previous work carried out by Zarek et al. described 3D printing of shape memory polymers that can be used in flexible electronic devices [22]. Integrating 3D printability to SMPs will allow us to explore the possibility of 3D printing SMHs.

Here, we report the design and synthesis of printable hydrogels (Fig. 1) which are composed of alginate and pluronic F127 (EO_{100}-PO_{65}-EO_{100}; PEO = poly (ethylene oxide), PPO = poly (propylene oxide)). F127 is a common material in 3D printing areas and it has a sol–gel transition near physiological temperatures [23,24]. Pluronic F127 diacrylate macromer (F127DA) also has this characteristic

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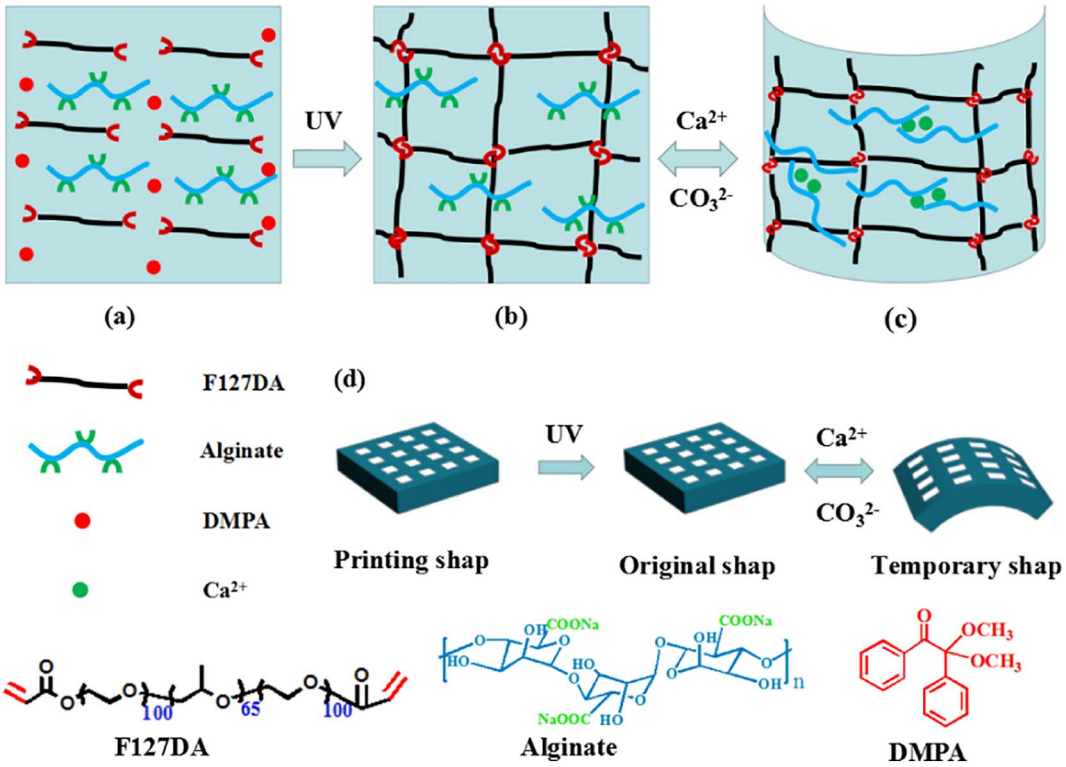

Fig. 1. The 3D printed shape memory hydrogel illustration. (a), (b), (c) The molecular mechanism of 3D printed shape memory hydrogels. (d) 3D printing memory hydrogel macro performance.

because it retains a PEO-PPO-PEO tri-block copolymer structure [25]. F127DA has been reported for the manufacture of multi-responsive [26] and self-healing [27] hydrogels with excellent mechanical properties. F127DA can be crosslinked under the excitation of a photoinitiator to form a stable hydrogel at room temperature. The hydrogel was printed (printing state) by a 3D printer. The original shape of the hydrogel (original state) was formed by UV cross-linking of F127DA. Alginate as a natural polysaccharide which can form a high viscosity aqueous solution was widely used in 3D printing because of its good biocompatibility [28–30]. We selected alginate as the other material because the chelating of alginate with Ca^{2+} imparts a shape memory function to hydrogels [31]. Ca^{2+} cross-linked sodium alginate fixes the temporary shape of the hydrogel (temporary state). The hydrogel was restored to its original shape (recovery state) by Ca^{2+} substitution which was by destroyed the cross-linked network of calcium alginate.

This study explores printing ink and printing parameters to create the excellent shape memory behavior of SMHs. The printing ink was designed by combining F127DA and alginate. The printing parameters were explored by calculating the expansion rate of the print lines. The shear modulus of hydrogels in the shape memory behavior cycle was analyzed by rheological experiments. It is also reported here that SMPs have good biocompatibility and can be rapidly released as a drug carrier.

2. Experimental sections

2.1. Materials

F127DA modified from F127, which includes material, pluronic F127 (Sigma, USA), acrylo acryloyl chloride (Aladdin, USA), triethylamine and dichloromethane (Tianjin Damao Chemical Reagents Company, China). 2,2-Dimethoxy-2-phenylacetophenone (DMPA) (Acros, USA) was dissolved in 1-vinyl-2-pyrrolidone (VP) (Aladdin, USA) as a photoinitiator. Alginate and methotrexate (MTX) were both purchased from Aladdin. All other chemicals were analytical grade and used as received without further purification.

2.2. F127DA-alginate ink fabrication

A critical first step was to develop printing ink, while the F127DA component was the principle determinant of initial print quality. Therefore, it was necessary to first determine the content of component F127DA. The ink in 3D printing compatibility experiment was tested over a range of 10%, 12%, 14%, 16%, 18% and 20% (*w/v*) F127DA with 4% (*w/v*) alginate. The shear viscosity of different concentrations of F127DA was measured at 25 °C. Then the ink was printed into lines to determine its expansion rate at different platform temperatures. The line expansion rate is the ratio of the diameter of the print line to the nozzle diameter. The line diameter was measured three times by a micrometer.

Alginate-Ca^{2+} coordination was the key to the shape memory function of the hydrogels. Accordingly, alginate was 2%, 4% and 6% (*w/v*) in the ink containing an equal amount F127DA, and the ink was used to print and evaluated its shape memory cycles to select the optimum alginate concentration. The quantitative shape memory cycle was determined according to the reported method [32]. Briefly, straight shapes were printed and cured with UV light for 3 min to form a hydrogel. It was bent into a U-form and immersed into 1% (*w/v*) $CaCl_2$ solution for 2 min. Then the deformed hydrogel was transferred into 2% (*w/v*) Na_2CO_3 solution to remove Ca^{2+} in the hydrogel. The shape memory cycles were evaluated by measuring the angle at specific time points. The shape fixity ratio (R_f) and shape recovery ratio (R_r) were defined by the following equations [33]:

$$R_f = \theta_t/\theta_i * 100\%$$

$$R_r = (\theta_i - \theta_f)/\theta_i * 100\%$$

While θ_i is the given angle, θ_t is the temporarily fixed angle and θ_f is the final angle.

The contents of the two components in the ink were determined by