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A nucleoside responsive diaminotriazine-based hydrogen bonding strengthened hydrogel

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ABSTRACT

Controlled or targeted release system responding to a specific biomolecular signal is an ideal goal in drug delivery. Herein, we fabricated diaminotriazine-diaminotriazine (DAT-DAT) hydrogen bonding strengthened functional hydrogels by one step of photo-initiated copolymerization which demonstrated unprecedented nucleoside responsive behavior. The hydrogen bonded hydrogels became increasingly swollen in response to thymidine due to much stronger competition of DAT-thymidine with DAT-DAT hydrogen bonding. Interestingly, thymidine was shown to facilitate drug release from the gels. This proof of concept study offers a new avenue to design and construct smart biomaterials capable of delivering target drug by virtue of nucleosides potentially from endogenously synthesized or indigested diet.

1. Introduction

DNA responsive hydrogels were reported recently. The biomaterial gels crosslinked with ssDNA-containing chains were able to shrink or swell in response to ssDNA samples, thus recognizing a single base difference [1]. Another interesting direction is to use aptamer-functionalized hydrogels for modulating delivery of growth factor induced by adding c-DNA, which is known to reverse the aptamer binding function [2]. Tan et al. [3] reported an adenosine sensitive aptamer-hydrogel system which became unstable and changed into solution phase since the aptamers selectively bound to adenosine targets and left only five base pairs to hybridize with one of the strands in the network. Compared with nucleic acid sensitive systems, base-pair responsive hydrogels have rarely been studied [4]. It is known that nucleosides which can be produced by denovo synthesis pathways are more abundantly supplied through ingestion and digestion of nucleic acids in the diet. Nucleosides have been suggested to play a role in the pathophysiology of nerve disorder symptoms [5]. Under pathological conditions, the levels of nucleosides change greatly in the brain [5]. This reminds us of harnessing nucleoside stimulus to deliver drugs to treat neurodegenerative disease.

In our previous works [6], we fabricated mechanically strong hydrogels based on the strategy of inter-diaminotriazine (DAT) hydrogen bonding. Poly(2-vinyl-4,6-diamino-1,3,5-triazine) (PVDT) has been demonstrated to reversibly and selectively bind nucleic acid bases and their derivatives through hydrogen bonding in water and the binding activity is enhanced with increasing number in the complementary hydrogen-bonding sites of the nucleobase towards the diaminotriazine residues [7]. Based on these features, we hypothesize that nucleic acid bases or nucleosides may be used as guest molecules to dissociate the hydrogen bonding of PVDT hydrogels through which the controllable permeation of drug would be achieved. In this proof of concept study, we will fabricate robust PEG-crosslinked PVDT hydrogel membranes, and investigate the permeation behavior of the model drug FITC-BSA through them, in response to two representative nucleosides, thymidine and cytidine in view of their better water solubility. The nucleoside responsive swelling of the hydrogels as well as delivery behavior of protein will be focused on.

2. Materials and methods

The preparation of PVDT-based hydrogels was briefly described in Supplementary Material. The permeation studies were performed using self-made side-by-side diffusion cells [8]. The PEG35KDA crosslinked PVDT hydrogel membranes were mounted between the two half-cells of the donor cell and receptor cell. The half-cell volume and the effective diffusion area of the membrane are 5 ml and 1.13 cm^2, respectively. 3 ml of PBS solution containing 3 mg model drug FITC-BSA and 4 wt% thymine was added to the donor cell, while a PBS buffer solution containing 4 wt% thymine was added to the receptor cell. At certain time intervals, 200 μL solution was taken out from the receptor cell for measurement of

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FITC-BSA permeation, and meanwhile 200 μL fresh 4 wt% thymine in PBS was replenished. To ensure constant temperature of the solution, the diffusion cells were incubated in an incubator at 37 °C. The amounts of released FITC-BSA (λ_{ex}=488 nm, λ_{em}=528 nm) were determined on a microplate reader (Synergy HT, BioTeck, America) using standard calibration curves. Mean values were determined from a total of three replicates in each case.

As a comparison, protein permeation experiment was also conducted in 2 wt% cytidine buffer and plain PBS, respectively.

3. Results and discussion

In our previous work [6], we demonstrated that PEG575DA crosslinked PVDT hydrogel was fragile, exhibiting 1.1–1.5 MPa tensile, more than 10 MPa compressive strengths and 100% break strain. In comparison, PEG35KDA crosslinked PVDT hydrogel was elastic and could withstand 400 kPa tensile, 700% break elongation, and compressive strengths in the magnitude order of MPa. In this study, we investigated the responsiveness of PEG-PVDT hydrogel to nucleoside. When the hydrogels swollen to equilibrium in PBS were transferred into thymidine solution, and reached new equilibrium, the mechanical properties were determined. We found the PEGDA crosslinked hydrogels only showed a negligible decrease in mechanical strengths. However, the swelling degree changed obviously. Fig. 1a shows the photograghs of PEG35K-PVDT hydrogel samples with 50 wt% VDT swollen in PBS and in different concentrations of thymidine solutions. Clearly, the diameters of hydrogels increase from 10.4 mm in PBS to 11.4 mm and 12.5 mm after being swollen in 2 wt% and 4 wt% thymidine solutions for 72 h, respectively. This result is in agreement with the variation in weight swelling degree as shown in Fig. 2a, which demonstrates the dynamic swelling of PEG35K-PVDT gels in response to thymidine. Fig. 2b shows that pure PEG35K hydrogel does not show noticeable increase in swelling ratio, suggesting that thymidine dissociates the hydrogen bonding among diaminotriazine moieties. The faster swelling rate of PEG35K-PVDT hydrogel with 20 wt% VDT may be attributed to its lower crosslinking density. By comparison, PEG575-PVDT hydrogels exhibit much less change in swelling ratio relative to PEG35K-PVDT hydrogels. Only less than 10% increase in weight occurs to PEG575-PVDT gel; while swelling ratio is increased by 20%-40% for PEG35K-PVDT gel in 2–4 wt% thymidine solution (Figs. 2a and 2c). As discussed previously,[21] the PEG575-PVDT hydrogels have a much higher crosslinking density relative to PEG35K-PVDT hydrogels, which leads to smaller mesh sizes, less than 1.5 nm, calculated from the method proposed by Canal and Peppas [9]. Inevitably, the smaller mesh size prevents thymidine molecules from penetrating into the hydrogel network, consequently resulting in only limited disruption of hydrogen-bonding.

Fig. 1b depicts the responsive mechanism of the PEG-PVDT hydrogels to thymidine. As the hydrogel is contacted with thymidine, the free thymidine molecules in the solution diffuse into the

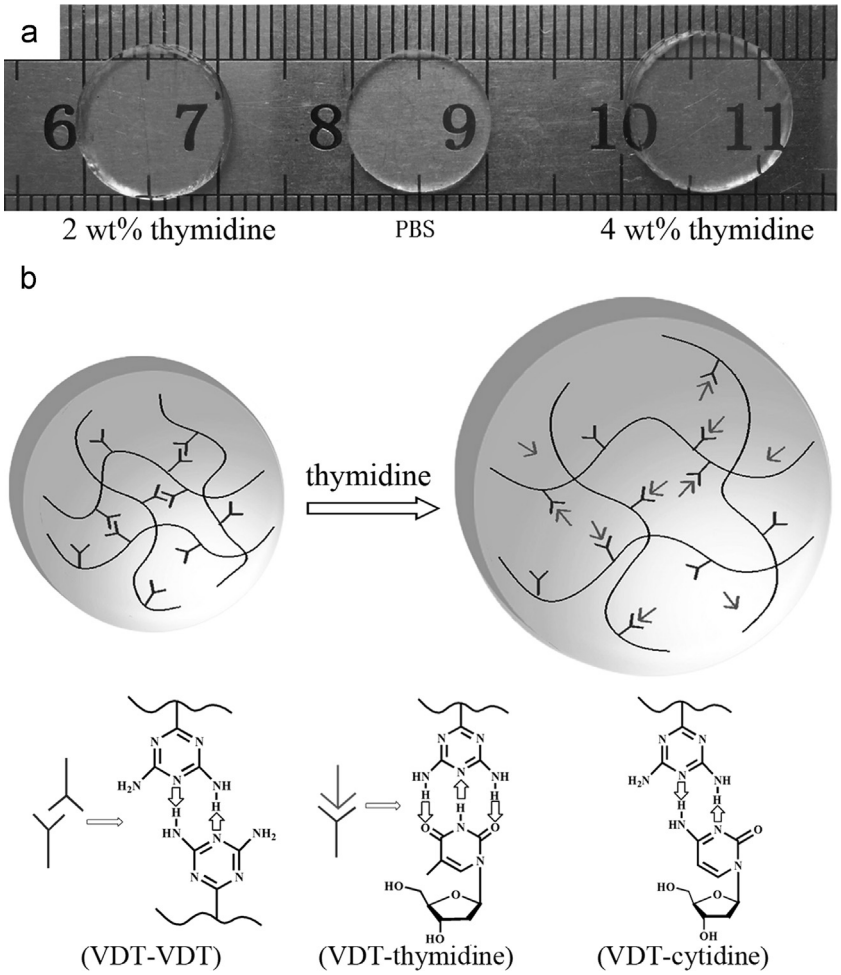

Fig. 1. (a) Photograghs of PEG35K-PVDT hydrogel swollen in PBS (middle), 2 wt% (left), and 4 wt% thymidine (right) solutions. (b)Schematic description of thymidine responsive mechanism of PEG-PVDT hydrogels, and hydrogen-bonding of 4,6-diaminotriazine (DAT) residue groups with various guest molecules.