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Controlled release from a mechanically-stimulated thermosensitive self-heating composite hydrogel

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ABSTRACT

Temperature has been extensively explored as a trigger to control the delivery of a payload from environment-sensitive polymers. The need for an external heat source only allows limited spatiotemporal control over the delivery process. We propose a new approach by using the dissipative properties of a hydrogel matrix as an internal heat source when the material is mechanically loaded. The system is comprised of a highly dissipative hydrogel matrix and thermo-sensitive nanoparticles that shrink upon an increase in temperature. Exposing the hydrogel to a cyclic mechanical loading for a period of 5 min leads to an increase of temperature of the nanoparticles. The concomitant decrease in the volume of the nanoparticles increases the permeability of the hydrogel network facilitating the release of its payload. As a proof-of-concept, we showed that the payload of the hydrogel is released after 5–8 min following the initiation of the mechanical loading. This delivery method would be particularly suited for the release of growth factor as it has been shown that cell receptor to growth factor is activated 5–20 min following a mechanical loading.

1. Introduction

Most of the efforts in the field of drug delivery systems has focused on the development of environment-sensitive polymers. Temperature and pH are commonly used environmental variables [1–4]. While pH can be coupled to variations within the body, temperature sensitive polymers are designed to be altered either externally [5–7] or are in off/on mode almost immediately after being injected in the body [8–10].

Temperature-responsive drug delivery systems are usually based on polymer hydrogels with a lower critical solution temperature (LCST) of around 38 °C. The drug is released when the tissue surrounding the hydrogel reaches a temperature slightly above normal body temperature [4,11]. While these systems work well for a number of applications, they also have some limitations. The need for an external means to cool or heat in many applications only allows limited spatiotemporal control over the delivery process.

As hydrogels have dissipative properties, their temperature may also be altered internally by viscous dissipation during cyclic loading, a process generally referred to as self-heating [12–14]. There are potentially several advantages of using the self-heating property of materials for drug delivery.

First, the drug release is coupled to a mechanical loading. As mechanical loading has been demonstrated to activate some growth factor cell receptors involved in the healing process of different tissues such as cartilage [15–18], the coupling of mechanical loading and drug release could induce some positive synergetic effects. Drug delivery system coupled to mechanical loading has already been developed, the drug being simultaneously released during the mechanical loading [19–21].

However, it is important to realize that cell receptors are not immediately activated following a mechanical loading. A delay of 5–20 min has been observed between the initiation of the mechanical loading and the activation of the cell receptor [22]. To induce a maximum potency, the release of a drug following a mechanical loading should then also be delayed by several minutes.

As the self-heating property induces a local temperature increase, which is related to the dissipative properties of the material and to the number of loading cycles, a delay can be obtained between the initiation of the mechanical loading and the temperature

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increase triggering the drug release. The use of dissipative energy generated in hydrogel could then offer a second advantage, which is the unprecedented spatiotemporal control over the delivery process. In particular, the use of self-heating property would be particularly suited for the delivery of growth factors to induce healing in a cartilage defect where the cells are naturally subjected to mechanical loading.

In this study, we establish the proof-of-concept that dissipative properties can be used as a new environmental variable to spatiotemporally control the release of a drug.

2. Materials and methods

2.1. Principle of dissipation used as an environmental variable

To explore the feasibility of using dissipative properties to control delivery from thermosensitive polymer based systems, we developed a unique hydrogel system consisting of two components: i) poly(2-hydroxyethyl methacrylate) (PHEMA)-based hydrogel matrix with highly dissipative properties and ii) poly(N-isopropyl acrylamide) (PNIPAM)-based thermosensitive nanoparticles, which are entrapped in the matrix hydrogel and shrink at temperatures above their LCST.

The principle used to temporally control the delivery of a payload following a mechanical loading is shown in Fig. 1A. Upon applying a mechanical load, a part of the mechanical energy is transformed into heat due to the dissipative properties of the hydrogel matrix. The heat produced by the hydrogel increases the temperature of the nanoparticles above their LCST and induces their collapse, which subsequently facilitates diffusion of the payload outside the hydrogel. The dissipative properties of the hydrogel can be modulated to link the duration of the cyclic loading with a targeted increase in temperature. Thus, a specific delay between the initiation of the mechanical stimulation and the release of a payload can be obtained.

HEMA is a hydrogel-forming material that is widely used in the biomaterials field [23,24]. Water content and crosslink density are the key parameters to control the mechanical and dissipative properties of these hydrogels [25,26]. The hydrogels can be obtained using different crosslinkers in a one-step photo-polymerization process [27]. The PHEMA hydrogels investigated in this study were crosslinked with ethylene glycol dimethacrylate (EGDMA) and contained 40% water.

2.2. Materials

2,2-dimethoxy-2-phenylacetophenone (Irgacure 651, 97%), ethylene glycol dimethacrylate (EGDMA, 98%), TWEEN® 80, Span® 80, N,N,N′,N′-Tetramethylethylenediamine (TMEDA, 99%), Ammonium persulfate (≥98%) and Xylene Cyanole FF were purchased from Aldrich and used as received. 2-Hydroxyethyl methacrylate (HEMA, 97%) and poly(ethylene glycol) dimethacrylate (PEGDMA, average M_n 550) were purchased from Aldrich and purified by basic aluminum oxide column chromatography to remove inhibitor. N-isopropylacrylamide (Aldrich, 97%) was purified

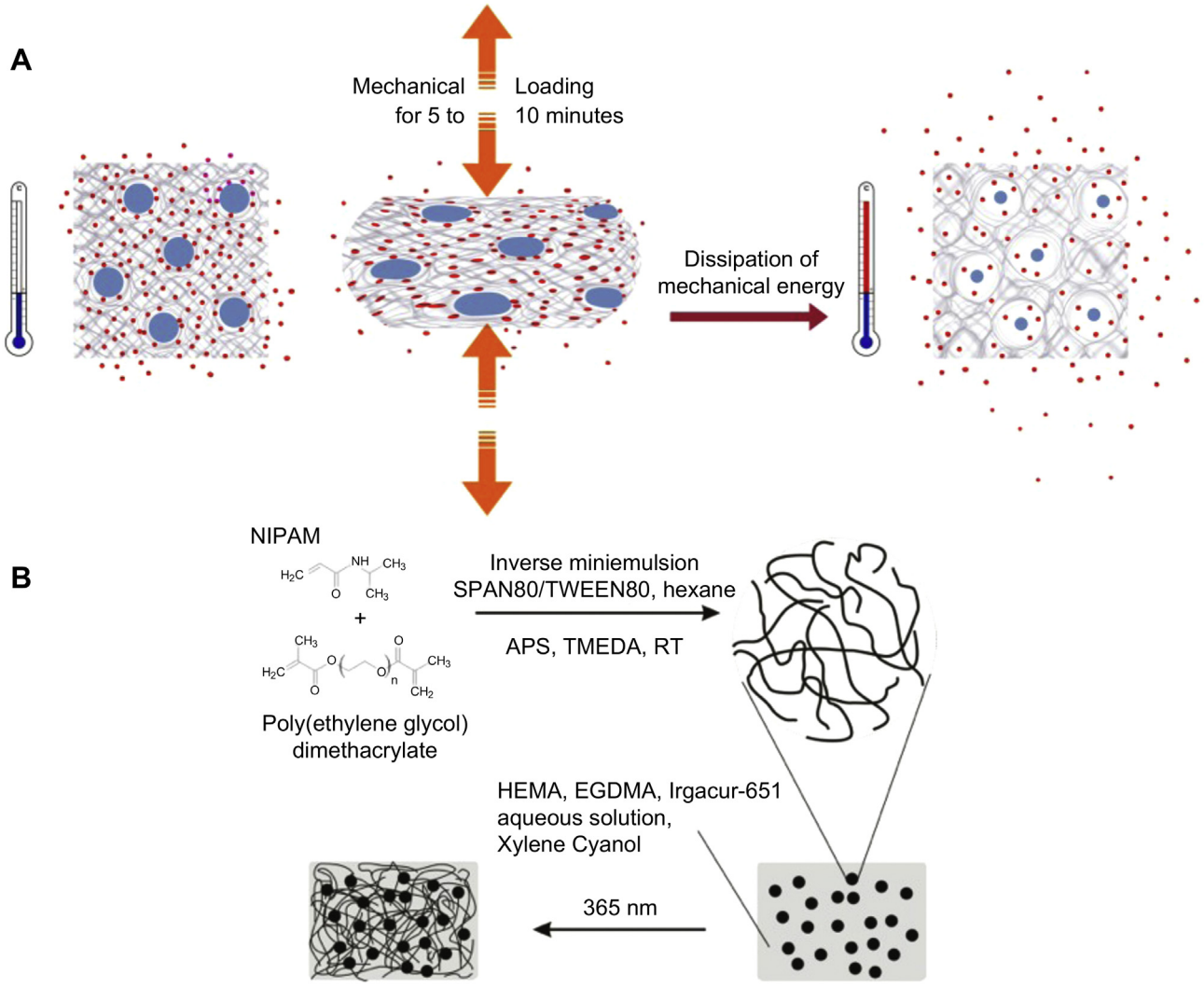

Fig. 1. A) Release of a payload from a thermosensitive delivery system using dissipation as an internal heat source. Thermosensitive nanoparticles (blue dots) and payload (red dots) are distributed randomly inside the hydrogel (gray). At temperatures below the LCST of the nanoparticles, only limited amount of payload can be released from the hydrogel. When the hydrogel is under a mechanical loading of 5–10 min duration, its dissipative properties induce a temperature increase, a process called self-heating. If the temperature rises above the LCST of the nanoparticles, they shrink, which increases the permeability of the hydrogel and facilitates the release of the payload. B) Synthesis of the composite hydrogel. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)