A Temperature-Sensitive Drug Release System Based on Phase-Change Materials

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Statement of Purpose: Stimuli-sensitive drug delivery is a promising strategy for achieving on-demand release of drugs. External and internal stimuli, including temperature, pH, and specific molecules, can all be utilized to regulate the release of drugs in various delivery systems.[1] Among them, temperature has been commonly used as a stimulus to trigger drug release due to the fact that local body temperature can vary in response to ambient conditions and diseases in some cases. However, the drug release systems fabricated from these materials have a number of shortcomings, such as non-biodegradability and significant toxicity (NIPAAm), the need of a high temperature process to load the drugs (PLGA and PEG block copolymers), the need of an additional heating system for initiation, and low encapsulation efficiency.[2] Therefore, the objective of present study is to demonstrate a new temperature-regulated drug release system by employing a class of phase-change materials (PCMs), including 1-tetradecanol with a melting point (m.p.) at 38-39 °C and dodecanoic acid with a m.p. at 43-46 °C.

Methods: (1) Gelatin colloidal particles (0.3-2 μm in size) containing FITC-dextran were prepared using a emulsification and solvent evaporation method. Uniform PCM-based beads containing the gelatin colloidal particles were fabricated using a fluidic device[3] by dispersing dried gelatin particles in a melted PCM phase for the discontinuous phase. (2) Uniform gelatin, chitosan, and PLGA microbeads were produced using the fluidic device[3]. A silicone mold was half filled with melted PCM and cooled down to room temperature (RT). Each kind of the microbeads made of gelatin, chitosan, and PLGA was placed on top of the solidified PCM. After solvent evaporation, more melted PCM was poured into the mold to fill the remaining space and cooled down to room temperature. For a dual PCM-based block, a dodecanoic acid matrix containing the uniform gelatin microbeads was fabricated first and then a 1-tetradecanol matrix was prepared on top of the dodecanoic acid matrix in the same mold. Release was initiated by adding warm water into a Petri dish containing either PCM beads or blocks, and recorded with a fluorescence microscope.

Results: The 1-tetradecanol beads were placed in a Petri filled with water at RT. Upon the addition of warm water (60 °C) and the rising of temperature, the 1-tetradecanol beads began to melt and the gelatin particles containing FITC-dextran leached out from the beads and eventually FITC-dextran was released into the warm water (Fig. 1A). We also fabricated and examined PCM blocks in the shape of a rectangular rod, containing uniform FITC-dextran-loaded microbeads. The 1-tetradecanol block containing the gelatin microbeads was placed in a Petri dish. As the temperature was increased, the PCM block began to melt and some of the gelatin microbeads containing FITC-dextran leached out from the matrix after t=60 s; more gelatin microbeads were observed at 90 s and subsequently dissolved in the warm water at 160 s; the PCM-based block was fully melted after 200 s (Fig. 1B). Figure 1C shows release profiles of FITC-dextran from the gelatin, chitosan, and PLGA microbeads encapsulated in 1-tetradecanol blocks at 37 and 39 °C. In all cases, FITC-dextran could not be released at 37 °C because the microbeads were fully surrounded by 1-tetradecanol that has a m.p. of 38-39 °C. At 39 °C, FITC-dextran was instantly released from the gelatin microbeads. By contrast, FITC-dextran encapsulated in the chitosan microbeads was released in a rather sustained manner due to the insolubility of chitosan in water at neutral pH. The PLGA microbeads showed the most sustained release pattern due to the hydrophobic nature of PLGA. Figure 1D shows the release profile of FITC-dextran from the gelatin microbeads encapsulated in the dual PCM-based matrix. FITC-dextran was released from the gelatin microbeads in the 1-tetradecanol matrix at 39 °C and then from the microbeads in the dodecanoic acid matrix at 44 °C.

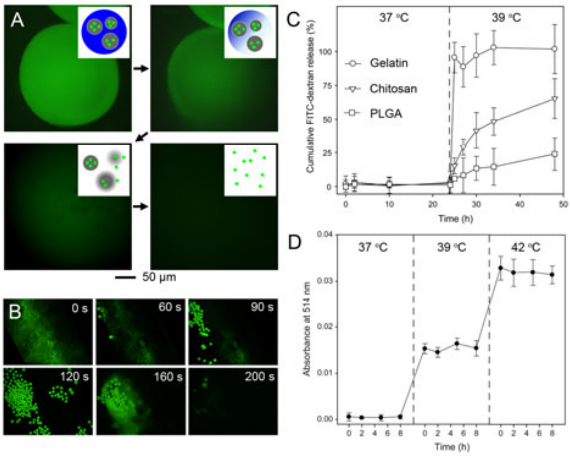

Figure 1. A, B) Fluorescence micrographs showing the release of FITC-dextran from PCM bead or block containing FITC-dextran loaded gelatin particles upon heating. C) The release profile of FITC-dextran from the gelatin, chitosan, and PLGA microbeads encapsulated in 1-tetradecanol blocks. D) The release profile of FITC-dextran from the gelatin microbeads encapsulated in the dual PCM-based matrix.

Conclusions: We have successfully demonstrated a new type of temperature-regulated drug release system based on PCMs. This new system has a number of attractive features: the simplicity in terms of fabrication procedure; no drug release below the m.p. of PCM; rapid response time to an ambient temperature, and precise control over the amount of released drugs. Such drug release system could be mainly utilized in the situations of elevated body temperature, including fever and inflammation.

References: [1] Qiu, Y., Adv. Drug Deliv. Rev. 2001, 53, 321. [2] (a) Ruel-Gariépy, E., Int. J. Pharm. 2000, 203, 89; (b) Hoare, T., Nano Lett. 2009, 9, 3651. [3] Choi, S.-W., Small 2009, 5, 454.