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Poly(NIPAAm-co-β-cyclodextrin) microgels with drug hosting and temperature-dependent delivery properties ☆

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ABSTRACT

One of the most important drawbacks of the thermosensitive hydrogels based on N-isopropylacrylamide (NIPAAm) is the lack of functional groups able to specifically bind drugs; moreover, these hydrogels are not biodegradable. In order to overcome these inconveniences, poly(NIPAAm-co-β-cyclodextrin) (poly(NIPAAm-co-β-CD)) microgels were obtained by cross-linking polymerization of the corresponding monomers. β-CD was first functionalized with an appropriate amount of vinyl groups, thus acting both as a co-monomer with hosting properties and as a biodegradable cross-linker. The volume phase transition temperature (VPTT) of the microgels was determined under simulated physiological conditions by measuring the swelling degree and by microcalorimetry. The microgels, due to their small size and high porosity, possess a relative rapid swelling/deswelling rate around the human body temperature. The hydrogels were loaded with the model drug diclofenac by inclusion within cyclodextrin cavity and the release studies were performed under simulated physiological conditions, below and the above the VPTT. In the presence of α-amylase (from *Aspergillus Oryzae*), microgels have showed a low degradation rate (15% of initial weight after 7 days), the erosion occurring especially at the surface.

1. Introduction

Controlled drug delivery systems have captured the attention of researchers in the last three decades [1–3]. Although great advances have been made in this area, these delivery systems are not appropriate for any type of disorder. As a result, self-regulated drug delivery systems have been designed and developed [4,5]. These systems have the capacity to perceive themselves small changes in normal physiological parameters and act to redress them.

Among the self-regulated drug delivery systems, thermosensitive hydrogels have a special place because they exploit small changes in the temperature of the human body and use these changes as triggering agents [6,7]. Most of the temperature-sensitive hydrogels are based on poly(*N*-isopropylacrylamide) (poly(NIPAAm)), indeed this polymer, in aqueous solution, possesses a transition temperature (called lower critical solution temperature; LCST), close to that of the human body [8,9]. Below the critical temperature, poly(NIPAAm) is in the hydrated state and is soluble, while above the critical temperature, the polymer is dehydrated and precipitates. Correspondingly, the hydrogel obtained from poly(NIPAAm) swells under the LCST and collapses above the LCST. This swelling/collapsing process is usually exploited for pulsatile release of drugs [10,11].

Three-dimensional hydrogels are usually obtained by dropping a polymer solution in a liquid heated to a temperature higher than the LCST [12]. The main disadvantage of these hydrogels is the lack of chemical and mechanical stability. In fact, hydrogels with good chemical and mechanical stability were synthesized by covalent [5] or radiation cross-linking method [13]. However, most of cross-linked hydrogels are not biodegradable since the water soluble *N*,*N*-methylenebisacrylamide is widely used as cross-linker in aqueous solution [14,15].

Biodegradable hydrogels were synthesized by cross-linking NIPAAm with a biodegradable PEG-co-PCL macromolecular cross-linker under UV irradiation [16]. However, these hydrogels do

Abbreviation: A-CD, acryloylated CD; AC, acryloyl chloride; CD, cyclodextrin; DMF, *N*,*N*-dimethyl formamide; DS, degree of substitution; DSC, differential scanning calorimetry; ESEM, environmental scanning electron microscopy; KPS, potassium persulfate; LCST, lower critical solution temperature; 3-MBA, 3-methylbenzoic acid; NIPAAm, *N*-isopropylacrylamide; PBS, phosphate buffer solution at pH = 7.4; TEA, triethylamine; TEMED, *N*,*N*,*N*′,*N*′-tetramethylethylene-diamine; VPTT, volume phase transition temperature.

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