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Research paper

Poly(N-isopropylacrylamide-co-hydroxyethylacrylamide) thermosensitive microspheres: The size of microgels dictates the pulsatile release mechanism

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ABSTRACT

Poly(N-isopropylacrylamide-co-N-hydroxyethylacrylamide) (poly(NIPAAm-co-HEAAm)) was prepared as a new thermosensitive copolymer possessing a sharp phase transition around the human body temperature. The effect of the copolymer concentration on the lower critical solution temperature (LCST) was determined under physiological conditions by cloud point (CP) and differential scanning calorimetric (DSC) methods. Then, thermosensitive microspheres were prepared from preformed copolymers by chemical cross-linking of hydroxyl groups with glutaraldehyde at a temperature situated slightly below LCST of the copolymer solution. The volume phase transition temperature (VPTT) of corresponding cross-linked microspheres was determined from swelling degree-temperature curve. The microspheres were loaded with model drug indomethacin by the solvent evaporation method. The DSC analysis proved that the drug is molecularly dispersed in the polymer network. Finally, the influence of the microsphere size on drug release was investigated. It was established that microspheres with the diameter ranging between 5 and 60 μm release the drug with almost the same rate below (in the swollen state) and above the VPTT (in the collapsed state). On the contrary, microspheres with the diameter ranging between 125 and 220 μm release a significantly higher amount of indomethacin below than above the VPTT. This different behavior is enough to assure a pulsatile release mechanism when the temperature changes cyclically below and above the VPTT. However, both small and large microspheres release a large amount of the drug during the collapsing process.

1. Introduction

Over the last decade, self-regulated drug release systems have been developed to improve patient therapy [1,2]. These advanced systems are able to release drugs whenever normal physiological conditions are disturbed, most of these systems being based on external stimuli-sensitive polymers [3,4].

Among stimuli-responsive polymers, temperature-responsive polymers are the most used in biomedical applications because they exploit small changes of temperature of the human body as triggering agents of drug release [5,6]. Poly(N-isopropylacrylamide) (poly(NIPAAm)) is the most representative thermo-responsive polymer because it shows a sharp phase transition around 32 °C in aqueous solution [7,8]. The temperature at which this transition occurs is called the lower critical solution temperature (LCST). Below the LCST, the polymer chain is in the hydrated state, is soluble, and adopts an extended coil conformation, while above the LCST the polymer is dehydrated, becomes insoluble, and adopts a globular conformation. Accordingly, the cross-linked hydrogels obtained from these linear polymers swell under the LCST and collapse above the LCST [9,10]. This swelling/collapsing process is usually exploit for controlling the delivery of drugs [11,12]. However, the biomedical applications of the gels usually involve the

Abbreviations: AIBN, N,N′-azobisisobutyronitrile; CP, cloud point; DSC, differential scanning calorimetry; ESEM, environmental scanning electron microscopy; GA, glutaraldehyde; HEAAm, N-hydroxyethylacrylamide; LCST, lower critical solution temperature; M_n, number-average molecular weight; M_w, weight-average molecular weight; NIPAAm, N-isopropylacrylamide; PB, phosphate buffer; PI, polydispersity index; poly(NIPAAm), poly(N-isopropylacrylamide); poly(NIPAAm-co-HEAAm), poly(N-isopropylacrylamide-co-N-hydroxyethylacrylamide); Tg, glass transition temperature; VPTT, volume phase transition temperature.

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