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ORIGINAL PAPER

Thermo- and pH-sensitive interpenetrating poly(N-isopropylacrylamide)/carboxymethyl pullulan network for drug delivery

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Abstract Interpenetrating polymer networks (IPN) consisting of pH-sensitive carboxymethyl pullulan (CMP) and thermosensitive poly(N-isopropylacrylamide) (PNIPAAm) were synthesized through a two-step procedure by chemical cross-linking of NIPAAm in the presence of CMP, followed by additional reticulation of the polysaccharide. The hydrogels were characterized by Fourier transform infrared spectroscopy, scanning electron microscopy and swelling measurements. Swelling properties of the hydrogels were studied at equilibrium, by investigating pH- and temperature-dependence, dynamic swelling ratio and pulsatile swelling-deswelling kinetics. It was found that IPN hydrogels responded to both temperature and pH changes and such stimuli-responsiveness was reversible. At pH 1.2 and temperature values lower than VPTT, the swelling ratios of IPN hydrogels are smaller than that of pure PNIPAAm because most of the carboxylic groups are protonated forming hydrogen bonds with other carboxylic or amide groups of PNIPAAm. Conversely, in phosphate buffer solutions at pH 7.4, the swelling ratios of IPN hydrogels are higher than that of pure PNIPAAm. In this case, the carboxylic groups of CMP are ionized; therefore, the hydrogen bonds are broken and the electrostatic repulsions lead to a more expanded network. The loading and release profiles of a model drug namely, diphenhydramine (DPH), were also evaluated. The results showed that the release rate of DPH was higher at pH 10 buffer solution than at pH 7.4 and 1.2, at 37 °C. In pseudo physiological conditions, DPH was quickly released from the hydrogel at 20 °C, and showed a sustained release profile at 37 °C.

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Keywords Interpenetrating polymer network · pH-sensitive polymer · Thermosensitive polymer · Hydrogel · Drug delivery

Abbreviations

APS	ammonium persulfate
BIS	N,N'-methylenebisacrylamide
CMP	carboxymethyl pullulan
DPH	diphenhydramine hydrochloride
ESEM	environmental scanning electron microscopy
GA	glutaraldehyde
IPN	interpenetrating polymer network
LCST	lower critical solution temperature
MCA	monochloroacetic acid
NIPAAm	N-isopropylacrylamide
P	pullulan
PBS	phosphate buffer at pH 7.4
TEMED	N,N,N',N'-tetramethylethylenediamine
VPTT	volume phase transition temperature

Introduction

In recent years, there has been an increased interest in the development of polymer hydrogels for controlled delivery of drugs [1–3]. Hydrogels are defined as three-dimensional networks of hydrophilic polymers which swell extensively but are not soluble in water. Furthermore, it was found that these hydrogels can respond to external stimuli and simultaneously show sudden changes in the physical and chemical nature of the hydrogel network [4, 5]. Among these hydrogels, pH- and temperature-sensitive hydrogels, have been intensively studied due to their great potential for biomedical and bioingineering applications, namely, pulsatile drug release, molecular separation processes, diagnosis, cell culture and bioreactions [6–8].