European Journal of Pharmaceutical Sciences 62 (2014) 86–95

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Poly(*N*-isopropylacrylamide-co-methacrylic acid) pH/thermo-responsive porous hydrogels as self-regulated drug delivery system

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form 6 May 2014
Accepted 9 May 2014
Available online 15 May 2014

Paper dedicated to the 65th anniversary of "Petru Poni" Institute of Macromolecular Chemistry of Romanian Academy, Iasi, Romania.

Keywords:
Self-regulated drug delivery system
Lower critical solution temperature
Volume phase transition temperature
pH/thermoresponsive copolymer
Stimuli-sensitive polymer

ABSTRACT

A dual drug delivery system based on a "biosensor" (pH-sensitive unit) and a delivery component (thermosensitive hydrogel) was developed. The pH/thermosensitive hydrogel is able to restore the thermosensitive characteristics after electrostatic interaction of the pH-sensitive units with selected biologically active compounds that act as triggering agents.

The poly(*N*-isopropylacrylamide-co-methacrylic acid) (poly(NIPAAm-co-MA)) was synthesized as an interesting pH/thermo-responsive copolymer by free radical polymerization method. Due to the presence of carboxylic groups in MA units, the copolymer loses its thermosensitivity at physiological pH and temperature. However, when the negatively-charged carboxylic groups of the pH-sensitive units interact electrostatically with the positively-charged drugs with hydrophobic character propranolol, lidocaine or metoclopramide, taken as model biologically active compounds, the copolymer restores the thermosensitive properties around the physiological pH and temperature. The poly(NIPAAm-co-MA) linear copolymer was converted into pH/thermo-responsive porous microgels using oligomers of NIPAAm above their LCST, as porogens. Accordingly, the swelling/collapsing processes of the microgels occur only after the interaction with the positively-charged hydrophobic drugs. The hydrophobic drug acts as a triggering agent and the pH/temperature sensitive hydrogel turns as a biosensor (pH-sensitive units) and a delivery component (thermosensitive hydrogel).

1. Introduction

Controlled drug delivery systems have been a major interest of researchers in the last thirty years (Kawashima et al., 2011; Wu et al., 2009; Ying et al., 2009; Yuan et al., 2010). However, although these systems were in vogue for a long period of time, they have not reached the high level of expectations and as a result a new generation of drug formulation called self-regulated drug delivery systems have been proposed (He et al., 2004; Vihola et al., 2002; Young et al., 1992). These systems are able to recognize changes in the parameters of normal physiological functions and act to address them. Most of self-regulated drug delivery systems are based on smart polymers. They are a group of materials that suffer a phase transition to small changes in external factors such as temperature (Choi et al., 2006), pH (Tan et al., 2007), light (Lin et al., 2010), and ionic strength (Park et al., 2007). Among them, polymers sensitive to temperature and pH are the most used because they exploit changes in temperature and pH as triggering agents for controlled release of drug (Fundueanu et al., 2005; Islam and Yasin, 2012). Most popular thermosensitive polymer is poly (*N*-isopropylacrylamide) (poly(NIPAAm)) because in water possess a sharp phase transition (lower critical solution temperature (LCST)) at a temperature close to body temperature (32 °C) (Heskins and Guillet, 1968). Under the LCST, the polymer is hydrated and soluble while above LCST, the polymer loses water

Abbreviations: AIBN, *N,N′*-azobisisobutyronitrile; APS, ammonium persulfate; CP, cloud point; ESEM, environmental scanning electron microscope; HEAAm, hydroxyethylacrylamide; KS, kanamycin sulfate; LCST, lower critical solution temperature; Lid, lidocaine; MA, methacrylic acid; MBAAm, *N,N′*-methylenebis-acrylamide; Met, metoclopramide HCl; MPA, 3-mercaptopropionic acid; NaB, sodium benzoate; NIPAAm, *N*-isopropylacrylamide; ONIPAAm, oligomers of poly(*N*-isopropylacrylamide-co-hydroxyethylacrylamide); PBS, phosphate buffer solution at pH = 7.4; PRP, propranolol HCl; TEMED, *N,N,N′,N′*-tetramethylethylene-diamine; VPTT, volume phase transition temperature.

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http://dx.doi.org/10.1016/j.ejps.2014.05.005
0928-0987/