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Evaluation of novel antiproliferative controlled drug delivery system based on poly(2-hydroxypropyl acrylate/itaconic acid) hydrogels and nickel complex with Oxaprozin

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ABSTRACT

A series of dual-sensitive poly(2-hydroxypropyl acrylate/itaconic acid) (P(HPA/IA)) hydrogels were synthesized and evaluated as potential highly effective antiproliferative drug delivery system. Investigated hydrophobic antiproliferative agent, Ni(II) complex with Oxaprozin, was successfully synthesized and efficiently loaded into the"'intelligent" P(HPA/IA) hydrogels. Swelling studies showed that loaded agent did not annul pH- and temperature-sensitivity of the investigated hydrogels. *In vitro* antiproliferative activity of investigated complex against human cervical (HeLa) and melanoma cancer (FemX) cell lines was tested. The results of *in vitro* release study at different pH values confirmed synthesized hydrogels loaded with investigated complex as a highly effective pH-triggered drug delivery system for the advanced anticancer therapy as well as for the targeted treatment of intestine/colon cancers.

1. Introduction

The seriousness of cancer and all costs associated with cancer therapy, both in human and financial terms, stresses the necessity for the development of novel anticancer drugs and treatments [1]. Cisplatin and the successive generations of platinum-based anticancer drugs (carboplatin and oxaliplatin) demonstrated that metal coordination complexes can be promising candidates for anticancer treatment [2]. The development of other transition metal complexes, as well as strategies of their controlled delivery, should result in the future generations of drugs that can overcome some of the disadvantages associated with cisplatin therapy (side-effects, widening the spectrum of activity, and resistance) [2].

An important challenge and one of the major trends in anticancer therapy is the formulation and controlled delivery of metal-based drugs. An innovative approach to the design of novel efficient anticancer drug delivery system (DDS) by combining transition metal based anticancer agent with stimuli-sensitive poly(2-hydroxypropyl acrylate/itaconic acid) hydrogels was presented. The Ni(II) complex with Oxaprozin (NiOXA) was synthesized as potential antiproliferative agent. Due to the fact that Ni(II) is a trace element that occurs in the reactive centers of many enzymes it can be expected with a great certainty that its complex with Oxaprozin possesses potential different biological activity [3–5]. Oxaprozin (OXA) belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs) and it was previously reported that transition metals complexes with oxa^- ligand exhibit additional antiproliferative activities [6]. In order to improve the anticancer therapy the evaluation of P(HPA/IA) hydrogels for loading and controlled release of Ni(II) based anticancer agent is presented in this work.

2. Materials and methods

The hydrogels were prepared by the free-radical crosslinking copolymerization [7]. The selected monomers were 2-hydroxpropyl acrylate and itaconic acid (IA). The mole fraction of IA were 0.0, 2.0, and 7.0%, and the resulting samples were labeled as PHPA, P(HPA/2IA), and P(HPA/7IA). The active compounds were synthesized according to the procedure described in the literature (Fig. 1(a)) [6].

Chemical composition of the hydrogels was analyzed by Fourier transform infrared (FTIR) spectroscopy using a FTIR spectrometer (BOMEM Michelfan MB-102 FTIR) in the wavelength range of 4000–400 cm^{-1}. Swelling measurements carried out in (acetate and phosphate) buffers mimicking biological fluids, in a pH range from 2.20 to 8.00, and in a temperature range from 30 to 50 °C.

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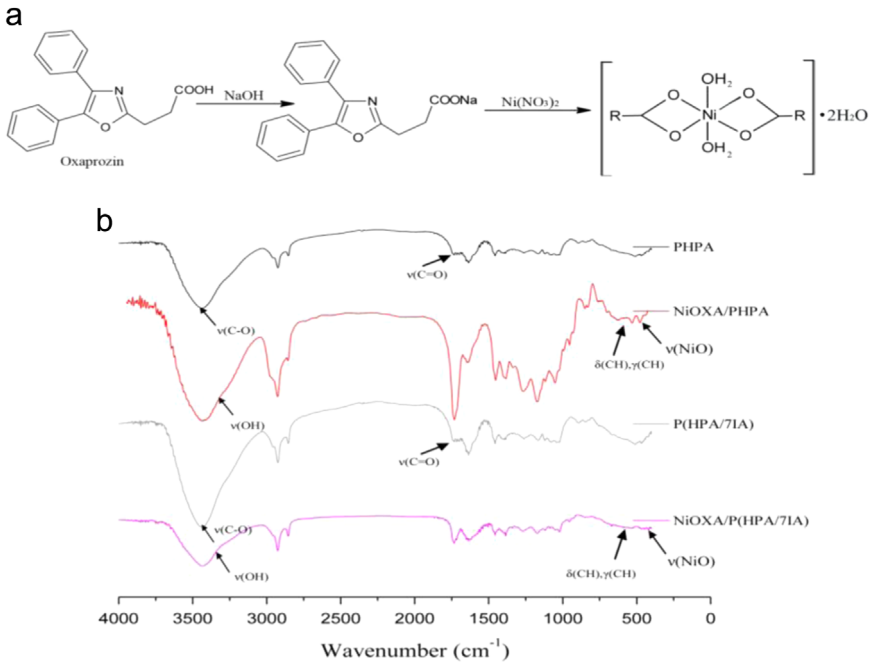

Fig. 1. (a) Synthesis route of NiOXA (b) FTIR spectra.

The amount of fluid absorbed as a function of time was monitored gravimetrically [8]. NiOXA was loaded into the hydrogels by a swelling-diffusion method [9]. The drug loading (*DL*, $mg_{drug}/g_{hydrogel}$) and entrapment efficiency (*EE*, %) were calculated by the following equations:

$$DL(\text{mg/g hydrogel}) = \frac{(\text{weight of drug in hydrogel})}{(\text{weight of drug free xerogel})} \quad (1)$$

$$EE(\%) = \frac{(\text{content of drug in hydrogel})}{(\text{theoretical content of drug})} \times 100 \quad (2)$$

In vitro NiOXA release study was performed in a buffer of pH 2.00 and mixture of buffer 7.40/dimethyl sulfoxide (DMSO). Drug loaded xerogels were placed in basket stirrer containing 30 ml of release medium, at 37 °C. The released drug was measured using a UV spectrophotometer (Shimadzu UV/Vis Spectrophotometer UV-1800). To evaluate the release kinetics, the first 60% of the obtained NiOXA release data of P(HPA/IA) hydrogels were fitted using the different kinetic models (Higuchi model, Ritger–Peppas, Peppas–Sahlin, and Peppas-Sahlin model when $m=0.5$) [9].

The synthesized OXA and NiOXA were evaluated for their cytotoxic effects on rat peritoneal macrophages by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Further, antiproliferative effect of investigated compounds on human cervical cancer (HeLa) and melanoma (FemX) cell lines by MTT assay were examined as previously reported [9].

3. Results and discussion

The FTIR spectra (Fig. 1(b)) revealed the characteristic ester peak at 1729 cm^{-1} (C=O stretching), the peak of OH group appeared at 3436 cm^{-1}, and aliphatic peaks in the range of 2900–3000 cm^{-1} for all samples.

The incorporation of NiOXA into the hydrogels was confirmed by the peaks at 447 cm^{-1} (ν(NiO)), 696 cm^{-1} (δCH, γCH) and a new weak band in the range 450–440 cm^{-1} that can be attributed to the M–O stretching vibration (this band verifies oxa^- coordination as O,O-donor ligand) [10]. An additional evidence for the incorporation of NiOXA, compared with unloaded hydrogel is the appearance of right shoulders in the range 3300–3200 cm^{-1} due to the presence of coordinated and uncoordinated water

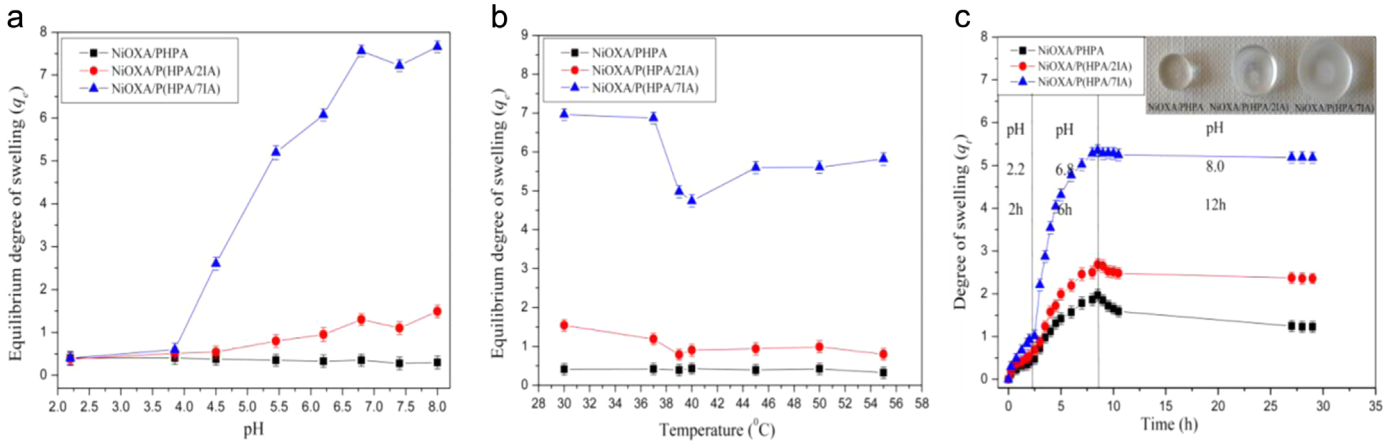

Fig. 2. (a) pH−, and (b) temperature-sensitivityof NiOXA-loaded P(HPA/IA) hydrogels, and their (c) swelling behavior in simulated gastrointestinal conditions.