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Interpenetrating polymer networks hydrogels of chitosan and poly(2-hydroxyethyl methacrylate) for controlled release of quetiapine

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ABSTRACT

Polymer networks interpenetrated by chitosan and 2-hydroxyethyl methacrylate (HEMA) were synthesized. The FTIR spectra confirmed crosslinking of chitosan and polymerization of HEMA. The swelling properties were studied at different pHs and depend particularly on the chitosan content of the material and the pH sensitivity of the network. DSC studies showed two vitreous transitions at approximately 98 °C and 155 °C, which correspond to the networks of *p*HEMA and chitosan respectively, demonstrating that the materials obtained are amorphous and interpenetrated. Creep-recovery and stress relaxation studies showed that the materials demonstrate viscoelastic behavior. Quetiapine was used as a pharmacological model for studies of controlled release, and it was found that the process is controlled by diffusion and by relaxation of the polymer network. Finally, the synthesized materials were degraded using lysozyme under simulated physiological conditions. A higher degree of degradation was observed in conjunction with an increase in the chitosan content.

1. Introduction

In the last few decades, polymers have found many applications in the biomedical field, including implantable devices (artificial hearts and bone screws), catheters and dialysis tubing, membranes for oxygenation and detoxing, systems for release of drugs, and membranes and porous scaffolds for tissue regeneration [1–3]. Recent interest in the development of polymeric materials has been focused on the development of smart systems capable of responding to environmental stimuli. Smart systems loaded with active molecules are especially useful for controlled release of drugs [4–6]. Hydrogels have been shown to be the most commonly used materials for this type of application given that they swell in aqueous media without dissolving, that they can incorporate different active compounds, and that some are biocompatible [7–11].

Hydrogels are three-dimensional networks formed by natural or synthetic polymers, physically or chemically crosslinked. Some hydrogels formed from natural polymers do not possess mechanical properties appropriate for use in controlled release systems. Yet, natural polymers contribute important properties including biocompatibility, biodegradability and biologically recognizable residues that support cellular activity. The structure of synthetic hydrogels can be modified to obtain properties adequate for the desired application. The combination of natural and synthetic polymers in a single network could exploit the advantages of the two systems [4].

Chitosan is a cationic polysaccharide composed of D-glucosamine and *N*-acetyl-D-glucosamine subunits. It is obtained principally through deacetylation of chitin and has been widely used as a matrix for controlled drug release in animals and humans [12]. It also possesses fungicidal and bactericidal properties [13,14].

HEMA (2-hydroxyethyl methacrylate) is one of the most commonly used monomers in medicine due to its low toxicity, biocompatibility, and high resistance to degradation and hydrolysis under physiological conditions [2,15–17]. *p*HEMA hydrogels have been used as scaffolds in tissue engineering, contact lenses, artificial skin, artificial organs, and drug delivery devices among others [5,6,18,19].

A network of interpenetrating polymers consists of a combination of two different polymer networks, lacking covalent bonds between them. In this way, a physical mixture that contains crosslinked polymers is obtained. This type of polymer is generated by simultaneous or sequential crosslinking of two different polymer systems, resulting in the formation of materials that exhibit properties of both components [20]. Various studies have been published detailing IPNs of diverse compositions that possess improved mechanical properties [21–24]. IPNs have also been prepared from natural polymers such as collagen [25], calcium alginate [26] and chitosan [27].

Lim et al. reported the design of contact lenses based on interpenetrated hydrogels of chitosan and *p*HEMA, with the aim of reducing

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the biological encrustation of proteins and improving hydrophilicity. The network was formed on a *p*HEMA hydrogel by coupling reactions of chitosan amines with EDTA [28]. Bayramoglu et al. prepared membranes from chitosan and *p*HEMA IPN hydrogels by photopolymerization and used them as adsorbents of Cd (II), Pb (II) and Hg (II) metal ions [29]. Dragan et al. obtained chitosan IPNs with acrylamide and HEMA by sequential synthesis and used them as lysozyme controlled release systems, demonstrating the potential of these pH sensitive systems in biomedical applications. In this case the HEMA network was obtained by cryogelation and the chitosan was crosslinked with poly (ethyleneglycol) diglycidyl ether [30]. Mahattanadul et al. prepared core-shell hydrogels based on chitosan and HEMA by emulsion polymerization and used them to encapsulate and release salicylic acid [31]. Han and co-workers prepared semi-IPN hydrogels from *p*HEMA, *p* (HEMA-co-SMA) and chitosan, with different molecular weights, crosslinked with EGDMA and PEGDA, and determined that the mechanical properties of the materials improved as the molecular weight of chitosan increased [32]. We found neither publications related to the synthesis of materials similar to those studied in this work nor their application in the controlled release of quetiapine. However, Shah et al. developed quetiapine fumarate (QF) based microemulsion (ME) with and without chitosan (CH) to investigate its potential use in improving bioavailability and brain targeting efficiency following non-invasive intranasal administration [33].

The hydrogels of chitosan have a good hydration capacity, thanks to the hydrophilicity conferred by their hydroxyl groups. However, this affinity to absorb water decreases its flexibility and mechanical resistance. This work proposed the combination of the chitosan with *p*HEMA to improve its mechanical properties, because poly(2-hydroxyethyl methacrylate) has a high mechanical strength and flexibility [2,15–19]. Other studies showed that the high water content of the hydrogels makes them compatible with living tissues. Research analyzing their effectiveness in inducing the healing process of lesions and tissue growth has been reported [34]. Azab et al. studied the toxicity of chitosan hydrogels for subcutaneous implantation in rats, reporting that no tissue damage was detected in different organs. Their results suggest that these hydrogels could be used as subcutaneous systems for the controlled release of radioisotopes in cancer therapy [35]. In addition, Lim Soo et al. studied implantable chitosan systems for the release of paclitaxel [36]. Khor and Lim published a review about different applications for implantable chitin and chitosan [37]. The goal of this study was to prepare IPN hydrogels containing different ratios of chitosan and *p*HEMA and to then study their structure, using FTIR, their thermal behavior using DSC, their mechanical properties, their swelling properties at differing pHs, and finally their application in a model of controlled drug release which could be used as a subcutaneous implant.

2. Materials y methods

2.1. Materials

Chitosan (low molecular weight, Sigma, > 98%, 75–85% deacetylated, molecular weight 50,000–190,000 Da), 2,2′-Azobis(2-methylpropionamidine) dihydrochloride (V50, Wako, > 98%), glutaraldehyde (JT Baker, 25% solution), glacial acetic acid (JT Baker, 99,7%), *N*,*N*′-methylenebisacrylamide (BIS, BIO-RAD, > 98%) and Lysozyme from chicken egg white (AMRESCO, Ultrapure grade) were used as purchased. 2-hydroxyethyl methacrylate (HEMA, Sigma, > 98%) was purified by vacuum distillation.

2.2. Synthesis of interpenetrating materials

The interpenetrated polymer network hydrogels were synthesized using seven different mass ratios (m_{CH}/m_H: 0/100, 30/70, 40/60, 50/50, 60/40, 70/30, 100/0). A solution of 3 wt% chitosan (CH) in 2% acetic acid was prepared and HEMA (H), the initiator (V-50, 1 wt%), and the crosslinking agent (BIS, 15 wt%) were added. To each of these solutions, glutaraldehyde (15 wt%) was added as a crosslinking agent for chitosan, generating a primary three dimensional polymer network at room temperature. Polymerization and crosslinking of HEMA was then carried out at 50 °C for 24 h. The resulting hydrogels were cut into discs and washed with water for one week. The discs were subsequently dried at room temperature until a constant weight was obtained.

2.3. Infrared spectroscopy

The xerogels of each material were characterized by FTIR spectroscopy of KBR pellets using a Thermo Scientific Nicolet 6700 spectrophotometer. Spectra were collected in the range of 4000 to 400 cm^{-1} and accumulating 32 scans. Each starting material was similarly analyzed.

2.4. Thermal analysis

Thermal analysis was performed with a DSC model Q2000 from TA Instruments. The samples were analyzed under an atmosphere of nitrogen and three scans were performed. The first was done from 3 to 95 °C to eliminate bound water, the second from 2 to 170 °C in order to observe any additional crosslinking, and the third from 20 to 220 °C to identify thermal transitions inherent to the material. All cycles were carried out at a heating rate of 5 °C per minute.

2.5. Mechanical properties

The rheological properties of the hydrogel were evaluated by an open system Bohlin C-VOR Instrument at 25 °C. The gap was adjusted depending on the thickness of each hydrogel. Two types of analyses were performed. First, a creep-recovery analysis was done in which deformation of the hydrogel was induced by applying a pressure of 30 Pa for 5 min, followed by 5 min of recovery time with no pressure applied. Second, a stress relaxation test was carried out in which a constant deformation of 0.5% was applied to the sample and variations in pressure and the shear modulus (G) were determined.

2.6. Swelling kinetics

Dynamic swelling studies were carried out by adding previously weighed xerogel tablets to a bath containing the appropriate buffer to achieve pHs of 5, 7.4 and 9 at 25 °C. The mass of the hydrogel was monitored as a function of time over three days and the grade of swelling (%W) determined using Eq. (1):

$$\%W = [(m_h - m_x)/m_h] \times 100 \quad (1)$$

where m_h and m_x are the masses of the hydrogel and the xerogel respectively. These studies were performed in triplicate for all the samples.

2.7. Controlled release of quetiapine

The materials selected for the controlled release studies were CH0H100, CH100H0 and CH30H70. The samples were placed in an aqueous solution of quetiapine (25 μg/mL) at room temperature in the absence of light for six days. Once the hydrogels were loaded with the drug and equilibrium swelling was obtained, they were dried at room temperature until a constant mass was achieved. The controlled release studies were performed at 37 °C, using 100 mL of 0.1 M phosphate buffer at a pH of 7.4, and monitored at 254 nm using a Shimadzu UV-1800 UV-VIS spectrophotometer at varying time intervals.

2.8. In-vitro degradation of the materials

In-vitro degradation studies were performed at 36 °C in a phosphate