

Synthesis and Characterization of Crosslinked Microparticles for Drug Delivery

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Abstract: Crosslinked chitosan and poly(hydroxypropyl methacrylate) microparticles containing a hydrophilic bioactive material, hydroquinone, were synthesized by suspension crosslinking and suspension polymerization, respectively and were extensively characterized. The produced microparticles had a spherical geometry and a smooth surface. The release rate of hydroquinone from the microparticles could be adjusted by varying the degree of polymer crosslinking as well as the initial polymer concentration. The degree of polymer swelling of the PHPMA microparticles could be properly modified by suitable adjustment of the degree of polymer crosslinking and of the composition of the solvent.

Keywords: Chitosan microspheres · Controlled release · Crosslinked microparticles · Suspension polymerization

Introduction

Hydrogels are three-dimensional hydrophilic polymers which have the ability to swell in water or aqueous solvent systems. The polymer structure is able to retain the solvents forming a swollen gel phase and, in cross-linked systems, will not dissolve regardless of the solvent (Kim *et al.* [1]). Concerning the release of drugs from hydrogel microparticles, various release profiles may be possible depending on the relative magnitude of the rate of polymer swelling to the rate of drug diffusion. Frequently, the rate of drug release from hydrogels can be regulated by controlling the cross-linking density and the extent of water swelling (Lee and Kim [2]).

Poly(2-hydroxypropyl methacrylate) (PHPMA) based microparticles have desirable properties such as non-toxicity, non-irritability and biocompatibility with living tissues. Such microparticles have

been prepared by various techniques, however suspension polymerization of hydrophobic monomers (*e.g.* methyl methacrylate, *etc.*) is relatively well studied (Kiremitci and Cukurova [3]).

Chitosan is a hydrophilic, cationic, natural polysaccharide and a hydrolyzed derivative of chitin, a biopolymer which is distributed widely in the nature (Peninisi [4]). Chitosan has attracted considerable attention as a new non-toxic polymer having favorable characteristics such as biocompatibility and biodegradability. Due to these properties, chitosan can be employed as a carrier for drug delivery systems.

In the present study, chitosan and PHPMA microparticles loaded with a hydrophilic bioactive material, hydroquinone, have been synthesized by suspension crosslinking and suspension polymerization, respectively. The size, surface morphology and swelling behavior as well as the release rate of the encapsulated active ingredient from the polymeric microparticles have been extensively studied.

soln of glutardialdehyde was used as the crosslinking agent (TAAB, EM 25%vol). The continuous organic phase consisted of light mineral oil (viscosity = 110–130cp, density = 0.844–0.89 g/ml) and sorbitan sesquioleate (Arlacel 83, HLB = 1.8, Merck) as the water-in-oil emulsifier.

The PHPMA microparticles were synthesized by 2-hydroxypropyl methacrylate (HPMA, Merck) and ethylene glycol dimethacrylate (EGDMA, Merck) as the crosslinking agent. Benzoyl peroxide (BPO, Merck) and polyvinyl alcohol (PVA, Nippon Gohsei) (Mn: 100 000, 98% hydrolyzed) were used as the initiator and the stabilizer, respectively. Toluene (Merck) was selected as the diluent. The hydrophilic active ingredient, hydroquinone, was kindly supplied by Lavi-pharm. All chemicals were of analytical grade and were used without any further purification.

Preparation of PHPMA Microparticles

Cross-linked PHPMA beads were prepared by a modified suspension polymerization technique. In this technique, polymerization was carried out in an aqueous phase containing PVA, which was used as the stabilizing agent. A three-necked flask (500 ml) with a blade type stirrer was used as the polymerization reactor. The reactant mixture con-

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Experimental

Materials

Chitosan microparticles were prepared from chitosan with a molecular weight of 750 000 (Fluka), while a 25%

taining the monomer HPMA, the crosslinker EGDMA and the diluent toluene, was added to the suspension medium. The reactor was flushed by bubbling nitrogen and then was sealed. The polymerization mixture was maintained at 70 °C for 3 h and then heated at 90 °C for an additional 1 h. After cooling, the polymeric microbeads were separated from the polymerization medium by filtration and washing. A series of polymeric beads with various degrees of crosslinking was prepared by changing the concentration of the crosslinker EGDMA. Hydrophilic active ingredients (such as hydroquinone) were loaded into the preformed gel microparticles by equilibrating a pre-weighed amount of PHPMA microparticles into a concentrated hydroquinone solution.

Preparation of Chitosan Microparticles

For the preparation of crosslinked chitosan microparticles by suspension crosslinking, 14 ml of a chitosan solution of various concentrations (*e.g.* 0.5, 1 and 2%) in aq. AcOH was initially formed. 0.1 g of hydroquinone was then dissolved in this polymer solution and mixed well. The mixture thus prepared was added dropwise into 100 ml of a liquid paraffin

solution containing 2% w/o sorbitan sesquioleate as the emulsifier. The water-in-oil emulsion obtained was stirred at 250 rpm for almost 1 h. Then a predetermined amount of a glutardialdehyde solution was slowly added into the w/o emulsion under continuous stirring to initiate the crosslinking of the emulsion droplets. Crosslinked microspheres were obtained after 2.5 h, recovered as a suspension in the oily continuous phase. The temperature of the process was adjusted to 25 °C. In order to remove the continuous organic phase and to collect the dried microspheres, centrifugation at 4000 rpm for 10 min was performed.

Characterization of Microspheres

The shape, surface morphology and mean size of the crosslinked chitosan and PHPMA microspheres were studied with the aid of a scanning electron microscope (SEM, JOEL Model JFM-840A), an optical microscope (Letz Mettallux 3) and a stereoscope (Nikon).

For the study of the release rate of the active ingredient from the chitosan and PHPMA microspheres, a preweighed amount of the microspheres was placed into 200 ml distilled water under stirring which was maintained at a constant rate throughout all the release ex-

periments. At fixed time intervals, samples were withdrawn from the solution and assayed spectrophotometrically (UV-Vis Shimadzu Instruments) at the wavelength of 290 nm of maximum hydroquinone absorbance. The total amount of hydroquinone released, M_{∞} , as well as the fractional hydroquinone released at time t , C_t/C_{∞} , were calculated from the experimentally measured absorbance values using a drug concentration – absorbance calibration curve.

Results and Discussion

The produced chitosan and PHPMA microparticles were completely spherical with a perfectly smooth surface (Fig. 1 and 2). The size of the chitosan microspheres was in the range of 10 to 100 μm , while the PHPMA microparticles were larger having a mean size in the range of 100 to 500 μm .

The effect of the degree of polymer crosslinking on the release rate of hydroquinone from the chitosan microspheres is depicted in Fig. 3a. Three different concentrations of the crosslinking agent (0.5, 1 and 2 ml of glutaraldehyde) have been employed. As the amount of the crosslinker increased, the release rate of the active ingredient from the gel micro-

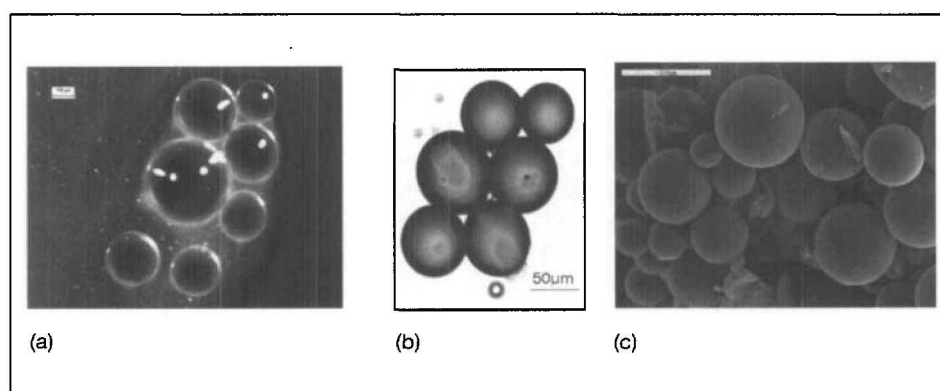


Fig. 1. Crosslinked chitosan microspheres under: (a) a stereoscope, (b) an optical microscope and (c) a scanning electron microscope.

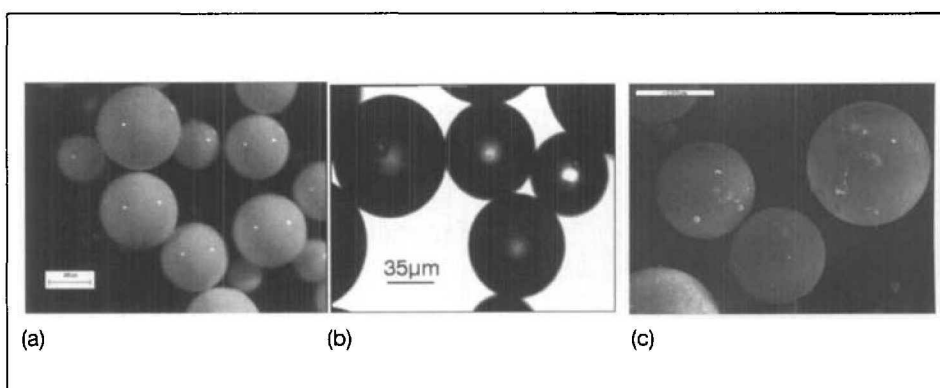


Fig. 2. PHPMA microparticles under: (a) a stereoscope, (b) an optical microscope and (c) a scanning electron microscope.

particles significant decreased. A steady-state release profile was obtained at the early stages of the release. It is apparent that, as the degree of polymer crosslinking decreases (at low concentrations of glutaraldehyde), the density of the polymer network also decreases, and thus the available free space for drug diffusion increases resulting in enhanced drug release rates (Bachtsi and Kiparissides [5]).

As shown in Fig. 3b, the concentration of chitosan in the initial polymer solution can also modify the release properties of the microparticles. When a more concentrated polymer solution was employed for the synthesis of the microspheres, the drug was more effectively entrapped into the polymer matrix, thus resulting in slower release rates. The higher release rates of hydroquinone were obtained from microparticles prepared by employing lower chitosan concentration.

Concerning the PHPMA microparticles, it was found that the PHPMA poly-

mer was more swellable in ethanol than in aqueous media: the equilibrium swelling ratio in ethanol ranged from 80% to 190%, while in water ranged from 5% to 40%. It must be emphasized that the swelling behavior of the polymer can be modified through control of its crosslink density. The more tightly crosslinked networks did not expand, either in water or in ethanol, as much as the loosely crosslinked ones.

The release profiles of the hydroquinone from PHPMA microparticles with variable degree of polymer crosslinking are depicted in Fig. 4a. It was shown that as the degree of crosslinking increased, the drug release rate considerably decreased. In general, it was found that the swelling and the release behavior of the PHPMA microparticles depend on the nature of the polymer (e.g. density of crosslinkage) and the characteristics of the external solution.

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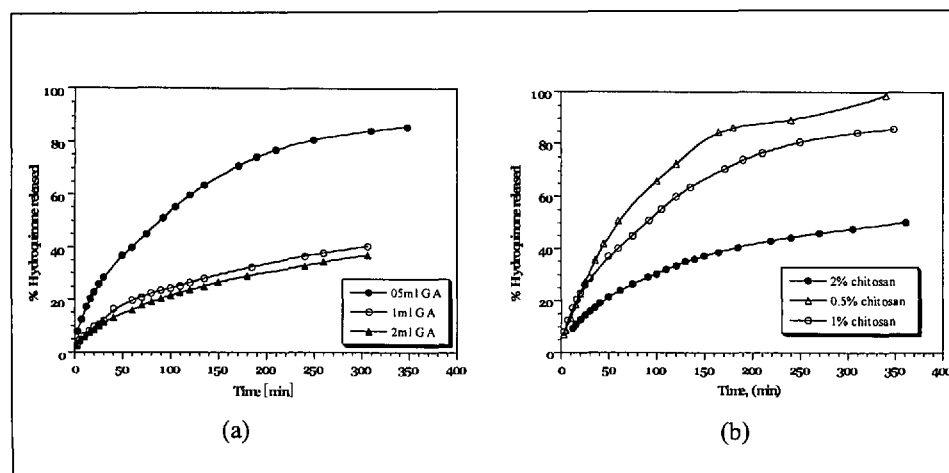


Fig. 3. Release profiles of hydroquinone from crosslinked chitosan microspheres: (a) effect of the degree of polymer crosslinking, (b) effect of chitosan concentration.

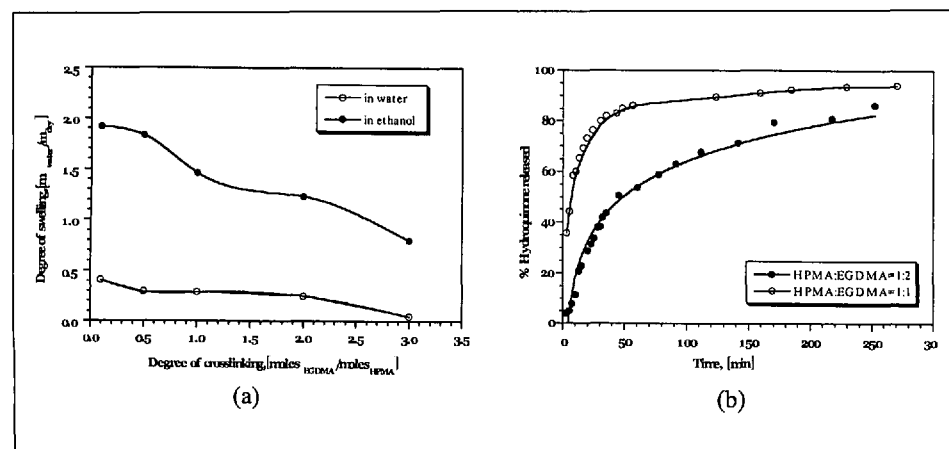


Fig. 4. (a) Effect of the degree of polymer crosslinking on the swelling of PHPMA microparticles in water and in ethanol, (b) effect of the degree of polymer crosslinking on the release of hydroquinone from PHPMA microparticles.