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Interpenetrating biopolymer network based hydrogels for an effective drug delivery system

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ABSTRACT

Discovery of hydrogels has resulted in developing competent controlled-release drug delivery systems. Present study describes the synthesis and characterization of novel pH responsive hydrogels of chitosan, hydroxyl ethyl cellulose (HEC) and polyol prepared by physical blending of the three components in different ratios. Vegetable oil derived polyol seems to act as a filler and cross linking agent. The synthesized hydrogels were characterized using FT-IR spectroscopy, thermo gravimetric analysis (TGA), Optical microscopy and scanning electron microscopy (SEM). Equilibrium swelling behavior of hydrogels in water and different buffers with pH values (2, 4, 7.3, and 8) indicated the sustained expansion of the films in different pH solutions.

1. Introduction

During the last three decades, momentous advances have been made in the controlled release drug delivery of therapeutic agents (Chilin & Metters, 2006; Gurski, Jha, Zhang, Jia, & Farach-Carson, 2009; Kopecek, 2007). The focus is now to design cost effective drug delivery systems and for the nontraditional routes of administration with the competence for self-regulating delivery.

Hydrogels have played a vital role in the development of controlled release drug delivery systems. Hydrogels are the three dimensional cross linked networks of water soluble polymers. These materials when placed in excess water are able to swell rapidly and retain large volumes of water in their swollen structures. The characteristics features of hydrogels are ability to alter their volumes and properties in response to the external stimuli such as pH, temperature, ionic strength and electric field. The low interfacial tension with the surrounding biological fluids and tissues make hydrogels biocompatible which minimizes the driving force for protein absorption and cell adhesion (Ganji & Vasheghani-Farahani, 2009). The high water content makes them biocompatible. However, high water content has limited their use as a drug carrier to a certain extent; because of dissolution before the drug can be delivered. To overcome this drawback the hydrogels have been cross linked with various cross linkers or hydrophobic groups to form interpenetrating networks (IPN's and copolymers). The hydrogels simulate some hydrodynamic properties of natural biological gels, cells, and tissues in many ways (Henriksen, Green, Smart, Smistad, & Karlsen, 1996). Hydrogels can be grafted onto biomaterials by physical adsorption, physical entrapment, graft coupling, and polymerization (El-Tahlawy, El-Rafie, & Aly, 2006; Sadeghi, 2010). The principal market of biomaterials is in the areas of cardiovascular implants, orthopedic implants, intravascular, urinary tract catheters, wound dressing, intra ocular lenses, biosensors, and controlled release devices. All of these biomaterials will improve their biocompatibility through coating with hydrogels (Bavaresco, Zavaglia, Malmonge, & Reis, 2002). The semi interpenetrating polymer network hydrogels of chitosan and poly-(acryl amide) (PAAm) on the other hand are well characterized (Kim, Shin, Kim, & Kim, 2005). It is an interesting material for pervaporation membranes or biomedical devices (Kalyani, Biduru, Sridhar, & Krishnaiah, 2006). The utilization of various natural polymers in drug delivery continues to be a subject of great interest. In the present study HEC, non-ionic carbohydrate polymer and another natural, non toxic and biocompatible chitosan obtained by alkaline deacetylation of chitin, which can be completely digested by the colonic bacteria have been used (Tozaki, 1997). These properties make chitosan a good candidate for the development of novel drug delivery systems (Molinaro, Leroux, Demas, & Adam, 2002). Despite the numerous advantages and unique properties of Chitosan, its films are quite brittle, which limits its application in dosage form

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Table 1
Feed compositions of the hydrogel network of (CH-HEC)–Polyol.

Sample code	Chitosan 4% (v/v)	HEC 2% (v/v)	Polyol 1% (v/v)
HY1	20	10	5
HY2	20	5	1.5
HY3	20	5	1
HY4	20	10	15

design. This problem can be overcome by blending it with the natural polymers like HEC which has good film forming ability. Such stabilization may involve some hydrophobic interactions (Lee, Kim, & Lee, 2000; Luo, Yin, KhutoryansKaya, & Kutoryanskiy, 2008). Novel pH sensitive hydrogel films of chitosan, HEC and polyol have been prepared and characterized by FT-IR, Optical microscopy, SEM and TGA. The swellings behaviors of these novel hydrogels and their degradability studies as the function of pH and time were performed to accomplish their potential as a candidate for an effective drug delivery system.

2. Materials and methods

2.1. Materials

Chitosan (448877-50G, Sigma Aldrich), HEC (G053006, Loba Chemie), linseed oil, glacial acetic acids, hydrogen peroxide, diethyl ether, acetic anhydride (Merck, India) were used as received. Linseed oil polyol was prepared using standard protocols (Sharmin, Ashraf, & Ahmad, 2007). Deionised water from Millipore mille U10 water purification system was used in the preparation of hydrogels and swelling experiments. 0.2 M (citric acid, trisodium citrate) and sodium phosphate buffers of required pH were prepared using different proportions of 0.2 M sodium dihydrogen phosphate and disodium hydrogen phosphate, other pH adjustments were carried using standard commercially available buffer capsules ranging from pH 4.0 ± 0.05, pH 7.3 and pH 9.0 ± 0.05.

2.2. Methods

2.2.1. Preparation of hydrogels of CH-HEC–Polyol

CH-HEC–Polyol hydrogel networks were obtained by simple mixing of the aqueous solution of (4%) chitosan in 1% acetic acid solution, HEC (2%), and polyol (1%) mixture in different proportions (Table 1). Initially the chitosan and HEC matrix is prepared followed by the addition of polyol. The reaction mixture was stirred for 8 h at room temperature on a magnetic stirrer. Synthesized hydrogel was stored at room temperature for 10 days to check its stability. Now thin films of dimensions 1 cm × 1 cm were casted on a separate glass plate.

2.2.2. FT-IR analysis of HEC-CH/Polyol hydrogels

The hydrogel films were dried under vacuum overnight till constant weights. Samples were then analyzed using model 1750 FT-IR spectrophotometer (PerkinElmer Cetus Instruments, Norwalk, CT).

2.2.3. Thermal analysis of HEC-CH/Polyol hydrogel

The thermal stability of the hydrogel films was determined using TGA (EXSTAR TG/DTA 6000) under nitrogen atmosphere at a heating rate of 10 °C/min. The TGA of dried samples (about 10 mg) was placed inside the hermitic aluminum lid. The thermal analyses were performed from 100 °C to 500 °C on the dried hydrogel sample under a dry nitrogen atmosphere.

2.2.4. Morphological analysis of HEC-CH/Polyol hydrogel films

The hydrogel samples swelled in various pH solutions (2, 4 and 7.3). Then they were plunged in liquid nitrogen and vitrified samples were quickly cut with a cold knife. Freeze drying of the gels was opted to maintain the porous structure without any collapse of the porous structure. The samples were fixed on the aluminum stubs with gold for 40 s for morphological analysis using Scanning electron microscope (LEO440 Model).

2.2.5. Optical microscopic studies

Lietz Optical Microscope Model (Metallux-3) was used to study the morphology of swelled and dried hydrogels at different magnifications.

3. Swelling studies

3.1. Swelling ratio measurement

Dynamic swelling ratio was calculated by gravimetric measurements. The hydrogel membranes were placed in test tubes in 25 ml water and various pH buffer solutions at 25 °C. The membranes were removed at different time intervals, carefully blotted with filter paper and weighed and again dispersed into the swelling medium. The swelling ratio was calculated using the equation:

$$\text{Swelling ratio} = \frac{\text{Swollen weight of the sample}}{\text{Dry weight of the sample}}$$

3.2. Equilibrium swelling ratio (EWS %) measurement

Dried CH-HEC–Polyol hydrogel polymeric membranes were left to swell in a solution of desired pH (4 and 7.3). The films were weighed before and after the contact of aqueous solutions. Swollen films removed from the test tube at regular intervals, were quickly and carefully dried superficially with tissue paper, weighed and placed into fresh solutions. Measurements were continued until a constant weight was reached for each sample. The % equilibrium weight of swelling (%EWS) was calculated using equation:

$$\%\text{EWS} = \frac{w_{\text{wet}} - w_{\text{dry}}}{w_{\text{dry}}} \times 100$$

where w_{wet} and w_{dry} were the equilibrium weight of swollen and dried hydrogels.

4. Biodegradation studies

4.1. Hydrolytic degradation

The in vitro degradation studies were performed at 37 °C in 0.1 M Na_2HPO_4/KH_2PO_4 buffer pH 7.4 containing 0.03% (w/v) NaN_3. Membranes of hydrogels were placed in 5 ml phosphate buffer prepared as above and incubated at 37 °C. The medium was changed daily and the pH was measured by pH meter. The degradation rate was indicated by the change of weight loss of hydrogel sample defined as

$$\text{Weight loss} = \frac{w_t - w_0}{w_0} \times 100$$

where w_0 and w_t were the weight initially and at specific time t.

The degradation was followed by determining the apparent weight changes at immersion in the buffer solution.

4.2. Soil burial test

A medium-term soil burial (Riaz, Vashist, Ahmad, Ahmad, & Ashraf, 2010) for a period of 6 months was carried out with hydrogel membranes in soil taken in a beaker under 30% moisture condition. For each composition three test specimens 1 cm × 1 cm were buried in soil taken in a separate beakers and weight loss was measured. A