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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

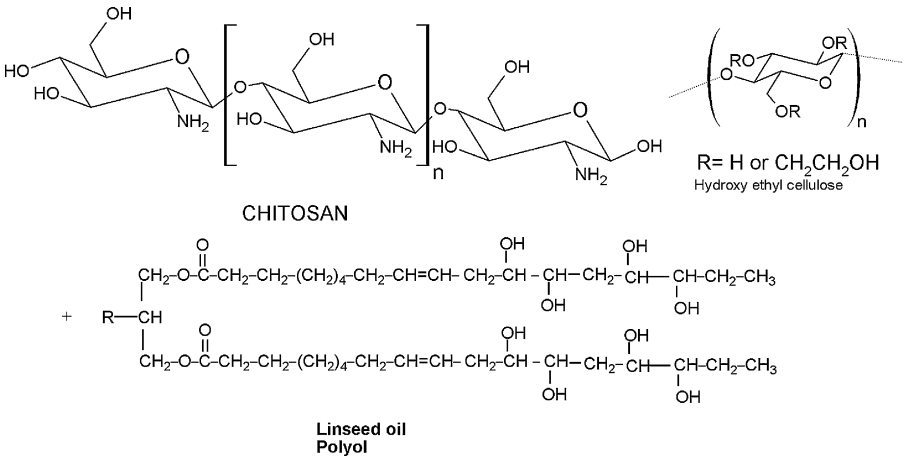

Fig. 1. (a) Schematic representation of the biopolymers used in the synthesis of CH-HEC/Polyol hydrogels.

long term study is favorable for characterizing the soil degradation of matrices (2 years). This short span study provided an insight into the degradation behavior of the hydrogel membrane.

5. Results and discussion

5.1. Structures and miscibility of the hydrogels

The hydrophobic interactions between different moieties of hydrogels can be attributed to the ionic crosslink's between cationic groups of NH_3^+ of chitosan and hydroxyl groups of HEC and Polyol. The structures and percentage of the three biopolymers used are shown in Fig. 1(a). The other reason is due to the hydrogen bonds formed in CH-HEC–Polyol hydrogel networks. These interactions are confirmed from FT-IR analysis (Fig. 2). All the interactions exhibit affinity towards water thereby enabling hydration of the polymer matrix which is essential for proton mobility. The hydrogen bonds prevent dissolution of hydrogels up to some specific time and may have important role in the pH sensitive swelling.

5.2. Hydrophobic interactions

5.2.1. Effect of polyol content in the hydrogel

The vegetable oil derived polyol has influenced the characteristics features like morphology, stability, and swelling kinetics of the hydrogels. The introduction of polyol induces a hydrophobic network into the matrix. The concentration of polyol has shown response in context with the viscosity of the hydrogels. The viscosity was increased as the polyol content was increased which results into a highly cross linked gel which cannot be casted on a glass sheet into membranes. The hydrogel formed with physical entanglements when kept for testing the stability showed a drastic reversibility and highly crosslinked gel transformed into a solution and when casted into membranes showed remarkable characteristics. Hence it was noteworthy that the polyol itself acted as a cross linker and thus formed a semi interpenetrating network. The

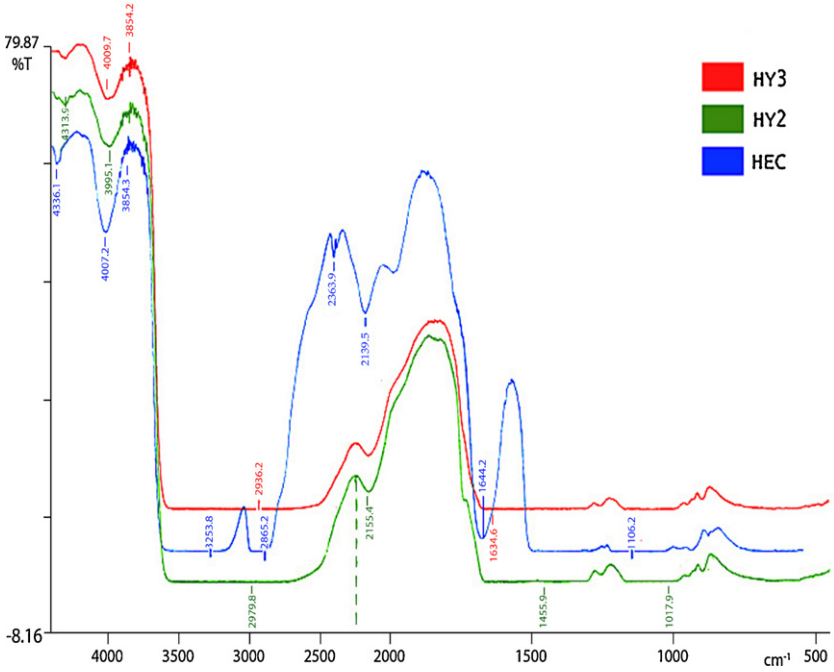

Fig. 2. FT-IR spectra of chitosan, HEC and CH-HEC/Polyol hydrogels.

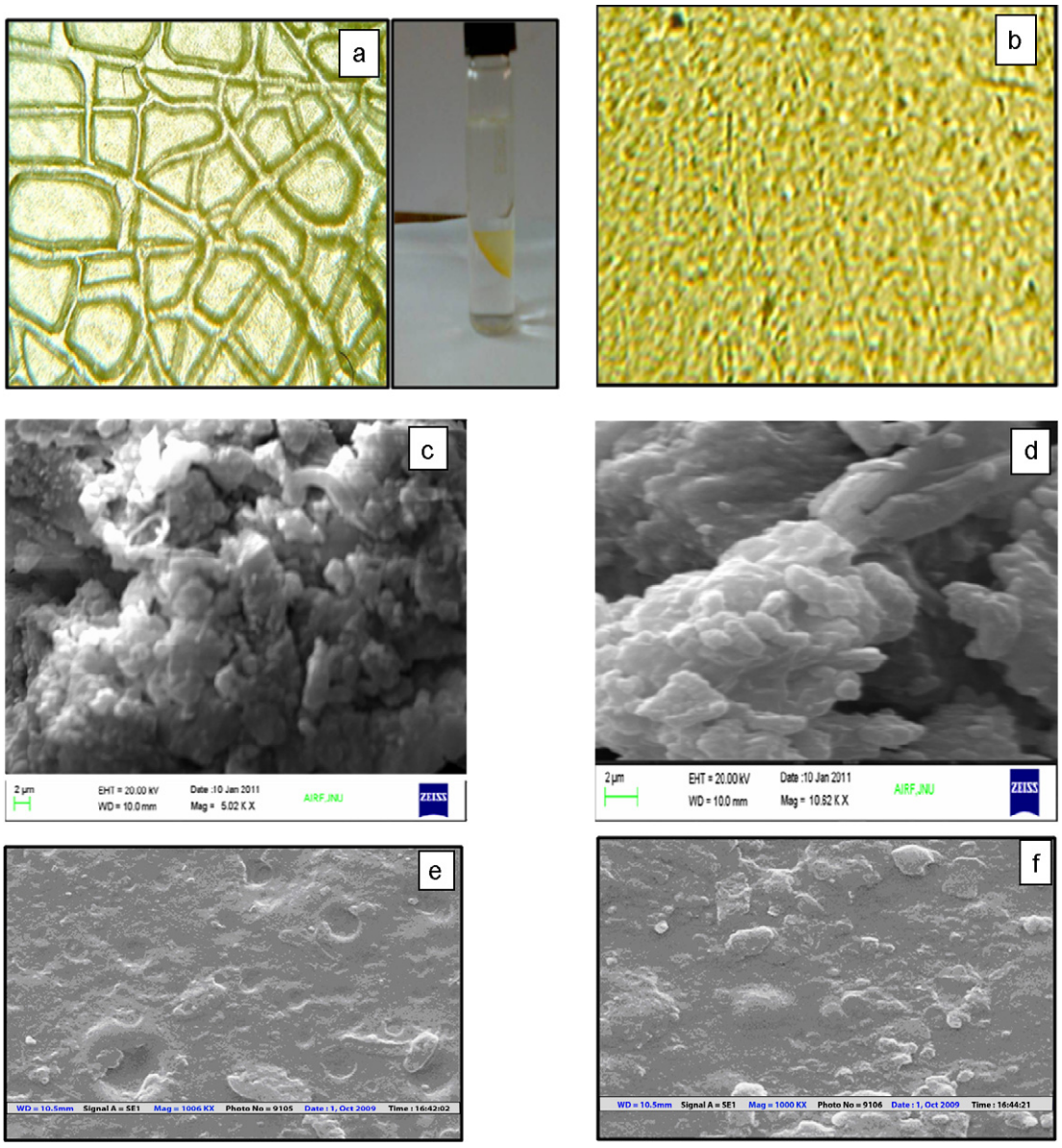

Fig. 3. (a) Optical micrographs of CH-HEC/Polyol in acidic (pH 1) environment at 37 °C; (b) Optical micrographs of the dried CH-HEC/Polyol hydrogel membrane at 25 °C; (c) SEM micrographs of freeze dried (liq N_2) samples of CH-HEC/Polyol hydrogel membrane at magnification 5.02K×; (d) SEM micrographs of freeze dried (liq N_2) samples of CH-HEC/Polyol hydrogel membrane at magnification 10.62K×; (e) SEM micrographs of the dried hydrogel membranes at the initial stages (2 weeks) of the degradation; (f) SEM images of the hydrogels after hydrolytic degradation at 4 weeks time.

minimal amounts of polyol addition into the CH-HEC matrix resulted in the formation of highly stable membranes. In recent years many types of polymer drug carriers have been designed to cover up the drawbacks of drug burst-release kinetics from the polymer matrix (Lin, Chen, & Luo, 2007). In the present study we have prepared novel hydrogels by incorporation of hydrophobic network into the hydrophilic network via interpenetrating polymer network technology. In these hydrogel films the moieties formed by hydrophobic network would slow down the drug release rate. The hydrophobic microenvironment can not only limit the swelling degree of hydrogels but can also act as reservoir of the drug from which drug can be released as a function of time (Bhattarai, Gunn, & Zhang, 2010). The drugs or solute having interactions with the polymer could efficiently reduce the release rates. In the present system with regard to the chain interactions, if the hydrophobic polyol segments are randomly distributed onto the hydrophilic polymer chain of the hydrogel, this may result in reversible physical cross linking. The cross-links are giving a response to the external stimuli pH as seen from the swelling studies. As the content of polyol was increased in the CH-HEC matrix, the formation of highly cross linked network is evident by the formation of interpenetrating networks (IPN) as observed during optical microscopic studies of hydrogels at pH 1.0 illustrated in Fig. 3(a). The occurrence of IPN may be due to molecular entanglements and/or secondary forces including ionic H-bonding or hydrophobic forces between the two monomers. Some non homogeneity was also observed as the content of linseed oil based polyol was increased which can be attributed to formation of clusters of molecular entanglements and hydrophobically or ionically associated domains. Free chain ends or chain loops also represent transient network defects in these physical gels.

5.2.2. *Morphological analysis of CH-HEC/Polyol hydrogel films*

The interior morphology of the dried CH-HEC/Polyol hydrogel films is shown in Fig. 3(b). The SEM analysis in Fig. 3(c) and (d) revealed presence of porous morphology in water swollen

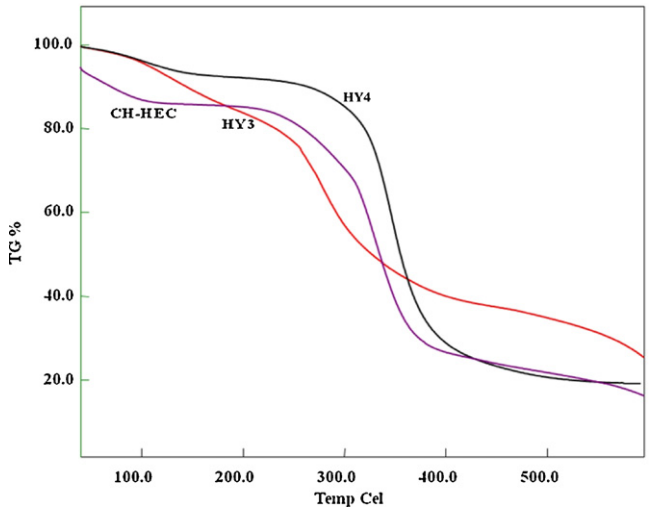

Fig. 4. TGA of the HEC-CH, HY3 and HY4 CH-HEC/Polyol hydrogels.

hydrogels. The porosity was increased when the films were dispersed in various pH solutions. Degradability of the hydrogel membrane was also studied by SEM analysis which revealed ruptured morphology as seen in Fig. 3(e) and (f). The membranes without polyol degraded in short interval of time in acidic pH whereas as the polyol content was increased in the hydrogel membranes the stability and the degradability time were increased.

5.2.3. FT-IR spectra of CH-HEC/Polyol hydrogels

The FT-IR absorption spectra of CH-HEC and CH-HEC/Polyol hydrogel samples are shown in Fig. 2. The IR spectra of CH-HEC showed a broad band from 3150 to 3650 cm^{-1} which may be due to hydrogen bonding between –OH groups of HEC and –NH and –OH groups of chitosan. The band is much broader incase of HY2 and HY3 because of increased intermolecular H-bonding due to –OH groups of the polyol. The broadening of the band increases with increase in polyol content. A band at 1644.2 cm^{-1} is due to the carbonyl stretching vibration of acetamide group in chitosan (Qu, Wirsen, & Albertsson, 2000). The band around 2145 cm^{-1} in all the three samples corresponds to –NH–C=O stretching. The IR spectrum clearly confirmed the formation of cross linked network through hydrogen bonding.

5.2.4. Thermogravimetric analysis (TGA) of CH-HEC/Polyol hydrogel

The TGA thermograms of HEC-CH, CH-HEC/Polyol HY3 and HY4 hydrogels are presented in Fig. 4. The TGA curve of HEC-CH hydrogel shows that its degradation occurs in two stages. The first stage continues up to 110 °C with a weight loss of about 13% while the second stage starts at 240 °C and reaches a maximum at 390 °C with about 70% weight loss. The first stage is assigned to loss of water and the second corresponds to breakdown of crosslink between Chitosan and HEC and ether linkages, hence the degradation of Chitosan and HEC (Neto et al., 2005). The TGA of CH-HEC/Polyol also shows two stages of degradation up to a temperature of 500 °C. The % wt. loss decreases and temperature of degradation increases with increase in polyol content which shows that the introduction of hydrophobic polygon in the CH-HEC matrix resulted in thermally stable membrane. The second stage of degradation resembles that of HEC-CH. Besides HEC-CH/Polyol also shows degradation beyond 510 °C which attributes to breakdown of hydrocarbon chains of polyol moiety.

6. Swelling mechanism

As the hydration of the membrane occurs the polymer-polymer interactions are disrupted. The comparison of the macromolecular relaxation rate with hydration is slower than the diffusion rate of water in the gel membranes, the second step that is relaxation process becomes rate limiting for the swelling mechanism. In such cases the process of swelling can be divided into two phase one is the glassy core and an already expanded swollen outer region, separated by an interphase. The swelling front proceeds from the outside towards the inside of the gel membrane at a constant rate. Consequently in the case of membrane with slab geometry the amount of absorbed water increases linearly with time (Hopfenberg, 1976). In the present study the dimensions of the hydrogel membrane changed abruptly when the membranes were immersed in acidic media. The expansion in the length and the breadth were about 72–80% until the degradation. Fig. 5(a) showed that films when kept at low pH solutions at room temperature showed instant swelling but degradation of the films was observed after 48 h. In contrast when films were kept in solutions of pH 7.3 and 8 at room temperature they showed a slow swelling behavior but stability of the films was not affected. No rupturing of films with higher content of polyol was observed during swelling studies up to 48 h at higher pH. Fig. 5(b) illustrates the pH responsive characteristic of CH-HEC/Polyol in different buffer solutions. The knowledge regarding the transport of water in polymeric hydrogels membrane is needed to improve the application of these materials in implantable drug delivery device (Zhao, Yu, Zhong, Zhang, & Sun, 1995). Work in this area has also been driven by the desire to use the membrane as rate controlling agent in delivery systems of bioactive compounds (Anal, 2007). The likelihood to functionalize cellulose-based hydrogels with bioactive and biodegradable extracellular matrix domains suggests that, such hydrogels might be best platforms for the design of scaffolding biomaterials in the field of tissue manufacturing and regenerative medication (Chen & Fan, 2008; Sannino, Demitri, & Madaghiel, 2009).

6.1. Equilibrium swelling ratio of CH-HEC/Polyol hydrogel films

Fig. 5(c) shows the relationship between EWS% and pH. The swelling behavior of the dried hydrogel films showed variation as the pH of the solution changes. The process of swelling of the prepared gels occurs with the absorption of water in the dried hydrogel. Firstly the water molecules hydrate the most polar hydrophilic groups, NH_2 and OH– of chitosan and HEC respectively. This kind of water is sometimes called primary bound water, after those groups are hydrated the chain begins to expand and as the hydrophobic groups are exposed to water molecules in this case hydroxyl groups of polyol, they interact via hydrophobic interactions leading to a kind of bound water coating in the surrounding of these groups. This kind of water is often known as the bound water and as these short range interactions of water with the polymer matrix backbone groups are satisfied then the network may imbibe additional water causing it to expand to an equilibrium swelling level. This additional water is known as free water or bulk water. The amount and the nature of the imbibed water in hydrogels determine absorption and diffusion of solutes through surface. HY4 hydrogels showed EWS% of 2462% at pH 2 whereas drastic change in the EWS% values at basic pH was observed. These hydrogels showed a very low specific solution content at basic pH as compared to acidic pH. This behavior may be due to the fact that at high concentration of the charged ionic groups in the hydrogel increases due to osmosis and charge repulsion (Singh, Narvi, Dutta, & Pandey, 2006).

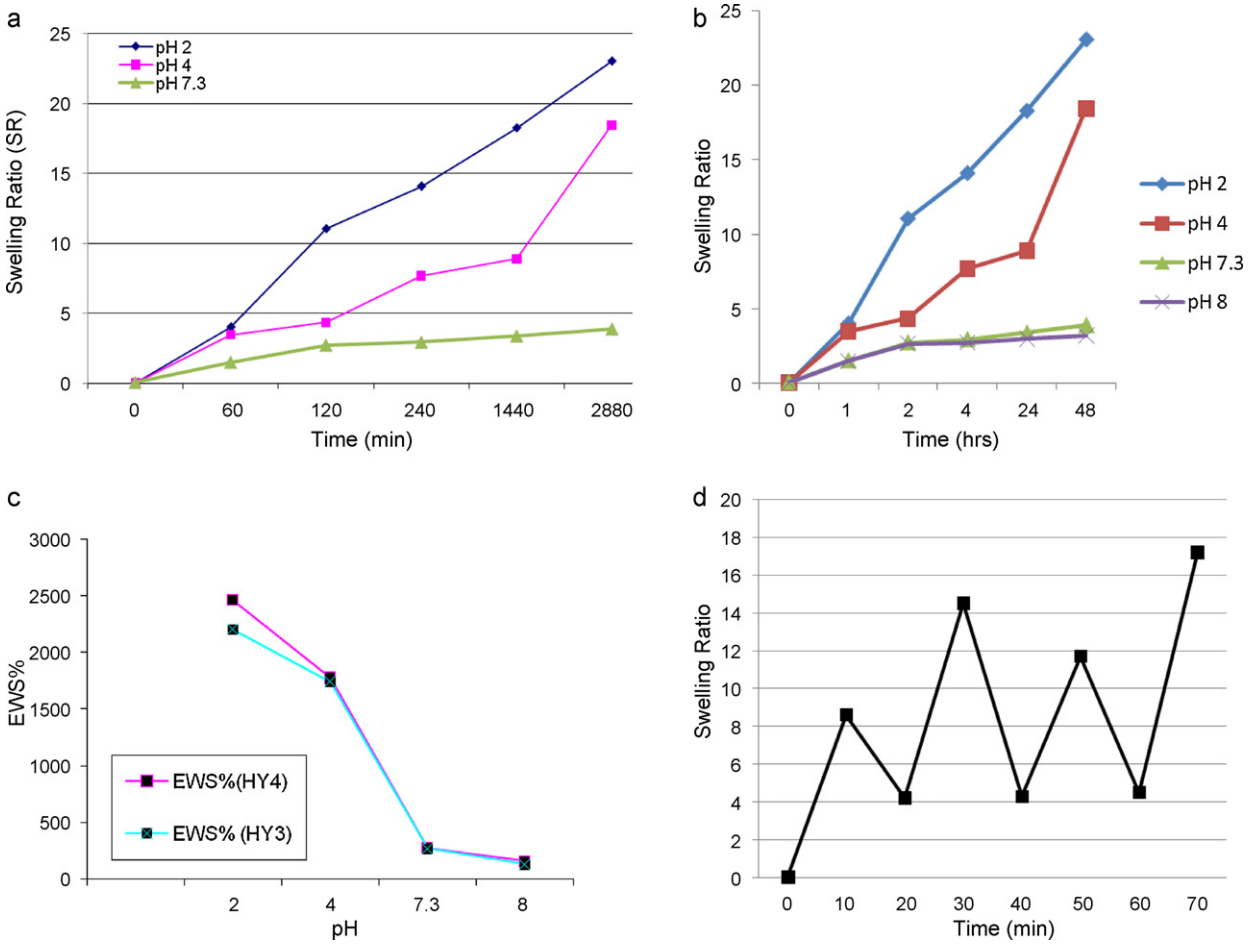

Fig. 5. (a) Swelling behavior of CH-HEC/Polyol in buffer solutions of pH 4, 2 and 7.3 at 37 °C; (b) pH responsive characteristic of CH-HEC/Polyol in different buffer solutions; (c) Equilibrium weight swelling (EWS %) behavior of CH-HEC/polyol hydrogels; (d) Pulsatile behavior of CH-HEC/Polyol Hydrogel membranes in pH 4 and 9 at 25 °C.

6.1.1. Pulsatile swelling response of the hydrogel membranes

Fig. 5(d) shows the pulsatile swelling behavior of the cross linked hydrogel membranes at 25 °C with alternating solution between pH 4 and pH 9 solutions. It was noted that the hydrogel membranes HEC-CH reached equilibrium state within 1 hr whereas HY04 membranes reach equilibrium swelling state in 24 h. Also the swelling ratio of the membranes with higher content of polyol at pH 4 was greater than the hydrogels without polyol or less content which was attributed to the formation of cross linked network and porous structure formed provided by the addition of polyol in them as confirmed by optical micrographs shown. In reference to the deswelling kinetics, during the initial stages the membrane undergoes phase separation and shrinks in the surface area. The upper layer forms a thick and dense layer and the entrapment of water inside the gels occur. This results in the prevention of any energy and mass transfer from the inner surface of the membranes. In case of the cross linked porous morphology the entrapment of water molecules occurs through this contemporary to the phase separation which has occurred on the surface into rapid deswelling as it was dispersed in pH 9. They were able to absorb and desorbs the swelling medium quickly upon the pH change from acidic to basic conditions quickly and vice versa. The structure of the super porous hydrogel with large number of pores connected to one another in the form of network channels was favorable for easy diffusion of the matrix thus contributing to its quick response towards pH change. The time of swelling was longer than that for deswelling which might be due to the restricted chain mobility of hydrogels membrane which was anchored at several points through molecular entanglements with polyol network because of the rapid pH sensitive behavior of the hydrogel membranes which was based on freely mobile chains. The swelling-deswelling studies confirmed that the hydrogels membranes with high content of polyol showed suitable mechanical strength and stability without collapsing during the on-off shrinkage and expansion changes.

6.1.2. Degradability studies

The effect of pH (2, 4 and 7.4) on degradation has been investigated for the prepared films. The hydrogel films of CH-HEC/Polyol were found to be completely degraded at low pH solutions 1, 2 and 4. There was subsequent weight loss in the films after EWS was attained. The introduction of acidic and hydrophilic monomers increases the water uptake and enhances the autocatalytic degradation (Heller, 1985). Here we have depicted hydrolytic and soil burial degradation which involve the hydrolysis of the functional group possessing the labile bonds. Degradability studies revealed that during the soil burial study initially the hydrogel membrane showed rapid increase in weight and subsequently weight loss occurred. Microorganism and fungi present in soil are responsible for the degradation of these hydrogel membranes as in the case of degradation of natural polymers. Soil microbes and fungi are generally responsible for the degradation of these membranes as in the case of degradation of natural polymers (Peanasky, Long, & Wool, 1991).

7. Conclusion

In this study it was demonstrated that the addition of polyol in chitosan and HEC matrix resulted in the formation of the membrane with improved stability and pH responsive characteristics. The miscibility of these hydrogels is a result of hydrogen bonding. FT-IR & SEM analysis revealed the formation of crosslinked structures containing hydrophobic moiety which act as cross linking agents enhancing the stability of the hydrogel network. The use of these hydrogel membranes may be explored for controlled release of pesticides of agricultural and public health importance with minimum impact on the environment as the matrix material was made up of biodegradable and sustainable resource based polymers.

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