A Novel pH Sensitive Porous Membrane Carrier for Various Biomedical Applications Based on pHEMA/chitosan: Preparation and Its Drug Release Characteristics

Gülay Bayramoğlu,[1] *M. Yakup Arıca*[2]*

[1]Department of Chemistry, Kırıkkale University, 71450 Yahşihan Kırıkkale, Turkey
[2]Department of Biology, Kırıkkale University, 71450 Yahşihan Kırıkkale, Turkey

Summary: The synthetic hydrogels based on pHEMA have been widely studied and used in biomedical fields. Numerous techniques exist for entrapment of drugs or proteins in the hydrogels. The suitable biomaterials for biomedical applications include poly(hydroxyethyl methacrylate), (pHEMA), and chitosan. In this work, a novel pH sensitive interpenetrating polymer networks (IPNs) were prepared in the membrane form by using 2-hydroxyethyl-methacrylate monomer (HEMA) and chitosan via UV initiated photo-polymerization in the presence of an initiator (i.e., α–α'-azo-isobutyronitrile; AIBN). UV-free-radical polymerization techniques are often used to synthesize hydrogels for controlled release applications. A series of HEMA and chitosan IPNs hydrogels were prepared and the equilibrium swelling studies were conducted to investigate swelling behaviors of the membrane according to the pH of the swelling medium. The swelling properties of the membrane were changed with the medium pH. The equilibrium water uptake is reached in about 60 min. The pHEMA/chitosan membrane thickness and density was measured to be 600 μm and 1.26 g cm^{-3}, respectively. Antibiotic release experiments were also performed with amoxicillin loaded pHEMA/chitosan membrane in physiological saline solution. The IPNs membrane loaded with 100 mg antibiotic (i.e., amoxicillin) g hydrogel released around 80 % of the amoxicillin in 10 h at pH 7.4. The presented well-characterized novel pHEMA/chitosan membrane is a potential candidate for transdermal antibiotic carrier or a support in bioseparation.

Keywords: amoxicillin; bioseparation; hydrogels; pHEMA/chitosan membrane; poly(hydroxyethyl methacrylate)

Introduction

The concept of controlled drug release has emerged from the need for effective management of diseases. Site-specific controlled release systems offer many distinctive advantages over classical methods of drug delivery. These include localized delivery of the drug to a particular

 DOI: 10.1002/masy.200351321

part of the body, assurance of treatment continuity in the nocturnal phase, drug stability, reduced need for follow-up care and optimized drug absorption.[1-3] There have been several reports over the use of hydrogels as controlled release system.[4] Hydrogels are three-dimensional hydrophilic structures that are capable of absorbing a large amount of water. These swollen networks have been of considerable interest in biomaterials as well as drug delivery applications due to their higher water content and soft nature. In the hydrated state, they have a mechanical behavior and water content similar to soft tissue, and as a result they exhibit excellent biocompatibility. Hydrogels may also show a swelling behavior depending on the external environments. These stimuli-sensitive hydrogels can exhibit dramatic changes in their swelling behavior of the network structure, permeability or mechanical strength in response to change in the pH, ionic strength, temperature and electromagnetic radiation.

pHEMA has also good mechanical strength and varying the concentration of pore forming agent in the polymerization mixture could modify the porosity of pHEMA hydrogels. Since pHEMA is considered non-ionic hydrogels, most of the studies reporting pH-sensitive swelling behavior involve modified pHEMA, either co-polymerised with acrylic or methacrylic acids. For pH sensitive hydrogels, either acid or basic pendant groups were contained in the network. The other component of the IPNs membrane is chitosan, which has a basic amine groups and is a natural polycationic polymer. Chitosan, (1→4)-2-amino-2-deoxy-β-D-glucan, is a polysaccharide obtained from chitin by deacylation process and has possesses useful properties such as non-toxicity, high biocompatibility and non-antigenicity that offer advantages for possible clinical uses.[5] The presented novel IPNs membrane has most of the useful properties for biomedical application. For example, it is highly hydrophilic and very inert toward microbial degradation and resistance to many chemicals due to its nature of both component of the network. The release of a drug through a network hydrogel based on pHEMA and chitosan is strongly affected by the water swelling capacity of the hydrogel.

A pH sensitive interpenetrating polymer networks (in the membrane form) consisting of pHEMA and chitosan in various proportions were prepared by UV initiated photo-polymerization. This novel pHEMA based IPNs membrane could be used a transdermal drug delivery systems. A model antibiotic (i.e. amoxicillin) release properties of these IPNs membrane were studied in a continuous release system. The capacity of amoxicillin loading and the drug release rate were compared under different conditions.

Experimental

The monomer 2-HEMA, and α–α-azobisisobutyronitrile were obtained from Fluka AG (Buchs, Switzerland). Chitosan and amoxicilline was purchased from Sigma (St Louis, USA). All other chemicals were of analytical grade and were purchased from Merck AG (Darmstadt, Germany).

The IPNs membrane synthesis was achieved by mixing a chitosan solution (1.0% chitosan solution in 1.0% acetic acid) with 2-HEMA monomer (2.0 mL) containing 20 mg AIBN. HEMA: chitosan ratio in the membrane preparation mixture was between 100:0 and 100:4. The solution was poured into a round glass mold, sealed and exposed to UV radiation under nitrogen atmosphere for 1.0 h at 25 °C. For the preparation of drug loaded IPNs membrane, the amoxicilline was added to the polymerisation solutions and the amount of amoxicillin per gram polymer was between (1:50, 3:50 and 5:50) were used to obtain various amount drug loaded IPNs membranes.

Amoxicilline-loaded IPNs membranes (about 300 mg) were placed in the continuous flow drug-release cell (8.0 cm^3). Physiological buffer solution (PBS, pH 7.2) was introduced through the bottom inlet port of the flow cell at a constant rate (25 $cm^3\ h^{-1}$) at 25°C. The effluent was collected at 1.0 h time intervals and the released amoxicilline was determined spectrophotometrically (Shimadzu, Model 1601, UV-Vis spectrophotometer, Japan) at 276 nm.

The scanning electron micrographs (SEM) of the membrane were obtained after coating gold using a JEOL (JSM 5600, Japan) scanning electron microscope.

FTIR spectra of the pHEMA and IPNs membranes were obtained by using a FTIR spectrophotometer (Mattson 1000 FT-IR, England).

The amount of chitosan in the IPNs membrane was evaluated by using an elemental analysis intrument (Leco, CHNS-932, USA), by considering the nitrogen stoichiometry.

The swelling behavior of the pHEMA and IPNs membranes was determined at 25°C and at various pHs (between 3.0 and 10.0) by using a gravimetric method. The pre-weighed dry samples were immersed in solutions with different pH values. After 2.0 h, the swollen membranes were removed and were weighed on a sensitive balance (Shimadzu, Model AX 120). The swelling ratio of the membranes were calculated by using fallowing equation:

$$\text{Swelling ratio}(\%) = \{(W_s - W_d) / W_d\}100,$$

where W_s and W_d are the swollen and dry weighs of membranes, respectively.

Results and Discussions

The microstructure of the networks, surface and the cross-sectional texture and membrane porosity were investigated by scanning electron microscopy. The surface properties of the pure pHEMA membrane exhibit a homogenous and highly porous structure. The IPNs surface morphology, on the other hand, displayed a smooth, channel like, and porous surface. The cross-section, however, did not much resemble the pure pHEMA structure. These observation, imply that HEMA may have used the chitosan macromolecule as a scaffold for the formation of the final product.

The pH sensitive swelling patterns of the pHEMA and pHEMA/chitosan (IPNs; ratio 100:4) were determined at different pH values. It was observed that the equilibrium-swelling ratio of the IPNs membrane was found to be higher to that of the pHEMA at acidic pH values. The equilibrium swelling ratio difference between the pHEMA and IPNs membranes was also increased as the medium pH decrease. It should be noted that an increase in the chitosan fraction in the IPNs membrane led to an increase in the equilibrium-swelling ratio at acidic pH values. These results clearly indicated that by varying the pHEMA:chitosan ratio in the IPNs membrane, it possible to regulate its swelling property at desired pH values. The change in the swelling behavior of the IPNs membrane is also significantly effect its drug release property.

The FT-IR spectra of the IPNs membrane have on absorption band different from that of the pHEMA at 1550 cm^{-1} representing N-H bending and C-N stretching in chitosan. The presence of chitosan is also in the IPNs membrane revealed by a strong absorption band between 800 and 1200 cm^{-1}, which is characteristic of the presence of pyranose rings.

It is a well-known phenomenon that hydrogels, due to their high water sorption capabilities, swell significantly in aqueous media. This creates an open-celled structure, which presents minimum resistance to the transport of solutes in their interior or exterior. These hydrogels offer the best system for controlled drug release studies, the open celled structure sometimes needs to be constricted using cross-linkers or blocker by a second hydrophobic/hydrophilic polymer with a capability to entrap in low molecular weight solutes. In the presented study, chitosan was introduced, as a blocker to reduce the pore size of the network at physiological pH value 7.4. Since chitosan is insoluble at neural and basic pH values, water penetration into the IPNs membrane was expected to decrease at these pH values, and thus resulted in a decrease in the release rate of amoxicillin.

When pHEMA/chitosan membranes were compared with chitosan free PHEMA, it was seen that the release duration was significantly extended by the incorporation of chitosan into the membrane, and this was more pronounced at higher chitosan ratio (Figure 1). It, thus, appears that chitosan has a significant influence on the release rate of amoxicillin at physiological pH value.

Another parameter which was expected to affect the release behavior was the drug:polymer ratio. The membranes prepared in this study are monolithic in nature, thus there is no separate barrier to restrict the diffusion of amoxicillin from the interior of the membrane to the surrounding medium. As such, the pHEMA and chitosan molecules act as entanglement sites and barriers to increase the tortuosity of the path of the diffusing solute. Thus, the lesser amount of drug or the more the barrier material, the slower will be the release from the membrane. When the results are examined (Figure 2), this is observed for the three IPNs-drug formulations. The apparent slow-release of amoxicillin from all these formulations during the release study seems to indicate that the release of amoxicillin from the IPNs membranes is dependent on the drug:polymer ratio.[6]

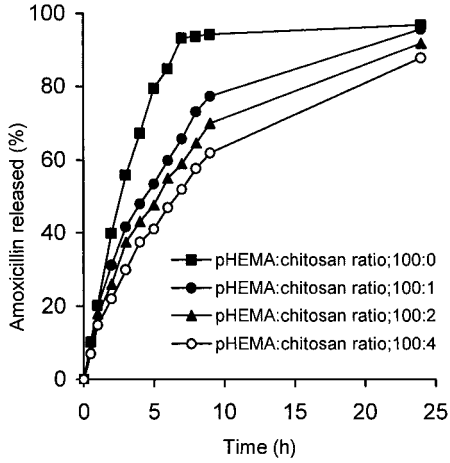

Fig. 1. Effect of chitosan content of IPNs membrane on the *in vitro* release rate (%) of amoxicillin in phosphate buffer pH 7.4 from pHEMA and pHEMA/chitosan membrane. In each formulation drug polymer ratio was 5:50 (or 100 mg amoxicillin per gram of the polymer).

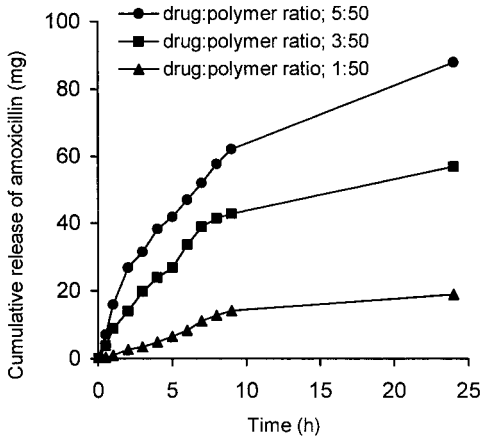

Fig. 2. Effect of drug:polymer ratio on the cumulative release of amoxicillin from IPNs membrane (IPNs composition; pHEMA:chitosan ratio; 100:4).

Conclusions

In the present study, IPNs hydrogels composed of pHEMA and chitosan with different composition were prepared by UV-photopolymerization. The release of amoxicillin membrane was sustained, and was significantly influenced by pHEMA to chitosan and the amoxicillin to polymer ratio. From these results, it is considered that the release of amoxicillin seems to be regulated by the HEMA:chitosan ratio. This study concludes that the pHEMA/chitosan membrane release patterns could be tailored according to need by varying the concentration of chitosan in the IPNs and thereby the membranes represent promising candidates for controlled release of antibiotic in the transdermal applications.

[1] I. Gursel, C. Balcık, M.Y. Arıca, N. Akkaş, V. Hasırcı, *Biomaterials* **1998,** 19, 1137.
[2] G. Bayramoğlu, B. Kaya, M. Y. Arıca, *Chem. Eng. Sci.***2002,** 57, 2323.
[3] D. Thacharodi, K.P. Rao, *Int. J. Pharmaceutics* **1995,** 16, 145.
[4] M. V. Risbud, A. A. Hardikar, S.V. Bhat, R.R. Bhonde, *J. Cont. Release* **2000**, 68, 23.
[5] D. Thacharodi, K.P. Rao, *Biomaterials* **1995,** 19, 1137.
[6] B. Arıca, M.Y. Arıca, H.S. Kaş, A.A. Hincal, V. Hasirci, *J. Microencapsul.* **1996,** 13, 689.