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Synthesis of A Novel Interpenetrating Polymer Network Hydrogel as Drug Delivery System

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Hossein Hosseinzadeh; Synthesis of A Novel Interpenetrating Polymer Network Hydrogel as Drug Delivery System

ABSTRACT

The present study is aimed at developing novel type of interpenetrating polymeric network (IPN) hydrogels of chitosan with poly(acrylic acid) for the controlled release of amphetamine drug. IPN hydrogels were synthesized by simultaneous polymerization/crosslinking of acrylic acid monomer in the presence of chitosan and crosslinker. The swelling properties and in vitro drug release characteristics of IPN hydrogels have been investigated in detail. Variation in composition of the IPN was achieved by varying the concentration of crosslinker. In addition, these IPNs were characterized for their pH-sensitive behaviour by equilibrium swelling studies. It was observed that the release of amphetamine was much higher at pH 7.4 compared to pH 1.2, indicating that the release system is controllable and can be as a release system for intestine specific drug delivery.

Key words: hydrogel, chitosan, acrylic acid, formaldehyde, swelling.

Introduction

Studies on multi-component polymers have been the subject of great interest, since they provide a convenient route to modify the properties in order to meet specific needs of drug delivery [1,2]. Among these methods, considerable interest has been devoted to the development of interpenetrating polymer network (IPN) hydrogels [3,4] for the controlled release of drugs. IPN is an intimate combination of two polymers both in the same network, which is obtained when at least one polymer is synthesized and/or crosslinked independently in the immediate vicinity of the other [5].

Recently, drug delivery systems based on natural hydrogels have been extensively explored to achieve the higher concentration of drugs in the specific region or tissue and the controlled release profile for extended time periods [6-9].

Hydrogels are special soft and pliable polymeric materials that can be absorb large quantities of water, saline or physiological solutions while the absorbed solutions are not removable even under pressure. In the swollen state, these become soft and rubbery, resembling a living tissue and some possess excellent biocompatibility.

In the current study, we investigated the synthesis and utility of an IPN hydrogel of chitosan with poly(acrylic acid) for the controlled release of amphetamine. Drug absorption and release capacities of hydrogel systems and influence of pH of the medium on the release properties were examined.

Amphetamines are powerful synthetic psycho-stimulants with a high potential of addiction. They increase vigilance and the ability to concentrate, temporarily elevate mood, and stimulate motor activity.

Chitosan, a natural poly(aminosaccharide), is non-toxic and easily bioadsorbable. This biopolymer is a weak base with an intrinsic pK_a of 6.5 and with gel forming ability at low pH. For several years, chitosan has been largely evaluated as a potential vehicle for drugs administered orally. The development of hydrogel matrices incorporated with chitosan for oral drug delivery is still a virgin area of study.

Experimental:

Preparation Of Hydrogel:

The IPN hydrogels were prepared using chitosan and poly(acrylic acid) in the presence of formaldehyde. In general, 0.50 g of chitosan was dissolved in 30 mL of distillated degassed 1wt% acetic acid solution and then 0.75g of poly(acrylic acid) was added to the chitosan solution and it was stirred to achieve a homogenous solution. The reactor was placed in a water bath preset at 70^{o}C.

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Desired volume of the formaldehyde solution was added to the mixture. The crosslinking reaction was allowed to proceed for 1h. The hydrogel was neutralized with NaOH solution (1N) to pH 7. Ethanol (300 ml) was added to the gelled product while stirring. After complete dewatering for 24 h, the hardened IPN hydrogel product were filtered, washed with fresh ethanol and dried at 50°C.

Determination Of Drug Loading:

IPN hydrogel (0.10 g) was immersed in 10 mL of the phosphate buffer solution in a 50 mL beaker for completely swelling. The swollen hydrogels were crushed in an agate mortar with a pestle and transferred into a conical flask, and then about 20 mL of the fresh phosphate buffer solution was added to the conical flask and the homogeneous mixture was sonicated for 20 min. The amphetamine solution was separated from the mixture after being centrifuged for 20 min at 5000 rpm. The amount of amphetamine was determined using UV spectrophotometer. The drug loading (%) was calculated using the following equation:

$$Drug\ Loading\ (\%) = \frac{Weight\ of\ drug\ in\ hydrogel}{Weight\ of\ hydrogel} \times 100$$

In Vitro Drug Release:

The samples (0.1±0.0001 g) were immersed into 50 mL of the release medium (simulated gastric and intestinal fluids, SGF and SIF) with different pH values (pH 1.2 or 7.4) at 37°C with agitation. At given time intervals, 1 mL of the release medium was removed using a syringe attached with a 0.45 Millipore filter and after suitable dilution the concentration of released drug was measured by UV spectrophotometer at 246 nm. The drug release percent was calculated twice using the following equation:

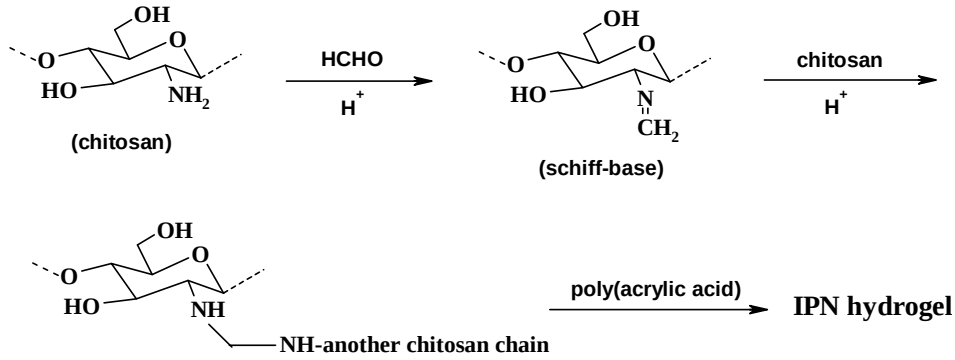
$$\mathrm{Re}leased\ drug(\%) = \frac{R_t}{L} \times 100$$

where L and R_t represent the initial amount of drug loaded and the final amount of drug released at time t.

Results and Discussion

Mechanism Of Hydrogel Formation:

The mechanism of crosslinking of chitosan with formaldehyde was illustrated in Scheme 1. At the first step, the schiff-base formation reaction takes place between amine groups of chitosan and formaldehyde. Then the imine group in acidic medium is reacted with the amine group of other chitosan chain and the crosslinks formed result in the IPN hydrogel in the presence of poly(acrylic acid).



Scheme 1. General mechanism for formaldehyde-crosslinking of chitosan to form IPN hydrogel.

Effect Of Formaldehyde Concentration On Swelling:

The swelling ratio as a function of formaldehyde concentration was investigated (Figure 1). Crosslinks is necessary to form a superabsorbent in order to prevent dissolution of the hydrophilic polymer chains in an aqueous environment. As the concentration of formaldehyde was increased, the water absorbency of the superabsorbent composite was decreased. This is due to a decrease in the space between the copolymer chains as the crosslinker concentration is increased.

Equilibrium Swelling At Various Ph Solutions:

Ionic superabsorbent hydrogels exhibit swelling changes at a wide range of pHs. Therefore, in this series of experiments, equilibrium swelling for the synthesized hydrogels was measured in different pH solutions ranged from 1 to 12. According to Figure 2, the two sharp swelling capacity changes can be attributed to high repulsion of $-NH_3^+$ groups in acidic media and $-COO^-$ groups in basic media. However, at very acidic conditions (pH≤2), a screening effect

of the counter ions, i.e. Cl^-, shields the charge of the ammonium cations and prevents an efficient repulsion. As a result, a remarkable decreasing in equilibrium swelling is observed (gel collapsing). Around pH 5, the carboxylic acid component comes in to action as well. Since the pK of the weak polyacid is about 6.4, its ionization occurring above this value, may favour enhanced absorbency. But under pH 6.4, at a certain pH range 4–6, the majority of the base and acid groups are as non-ionized forms, so hydrogen bonding between amine and carboxylic acid may lead to a kind of crosslinking followed by a decreased swelling. At higher pHs, the carboxylic acid groups become ionized and the electrostatic repulsive force between the charged sites (COO^-) causes increasing in swelling. Again, a screening effect of the counter ions (Na^+) limits the swelling at pH 8–12.

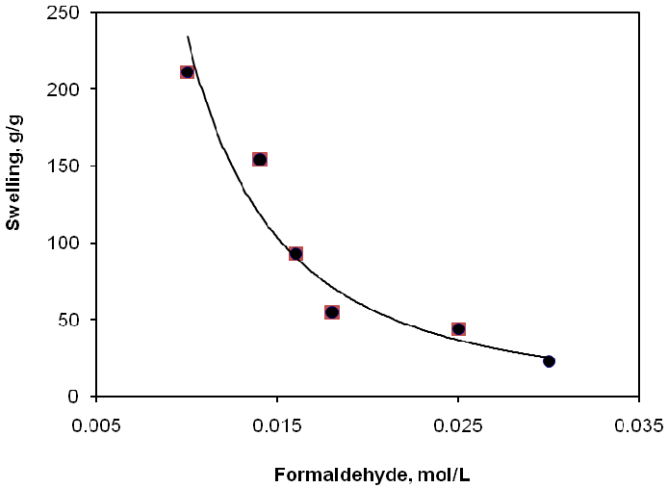


Fig. 1: Effect of the crosslinker concentration on water absorbency of the IPN hydrogel.

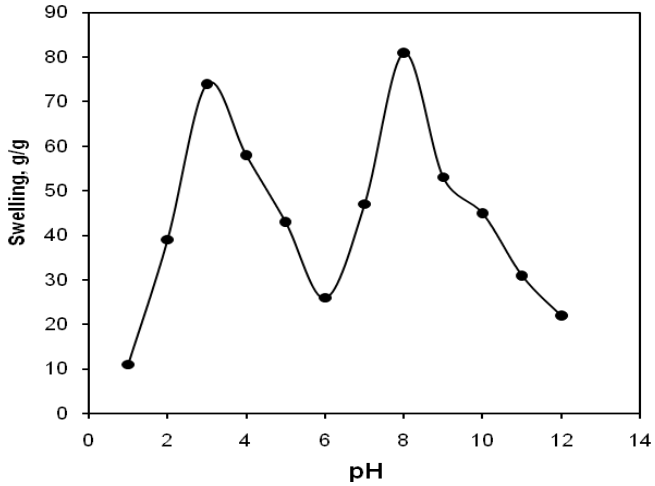


Fig. 2: Effect of pH of buffer solutions on swelling capacity of IPN hydrogel.

In Vitro Release Behaviour Of Hydrogels:

In this series of experiments, we investigated the drug release behaviour form this system under physiological conditions. The release rate experiments were performed in SFG (pH 1.2) and SIF (pH 7.4) solutions at 37°C (Figure 3). As can be seen from Figure 3, when pH of the medium is 1.2, the cumulative release ratio of amphetamine from the test hydrogels is 30% at the end of the experiment (20h), whereas 66% of the loaded drug is released within 10 h in pH 7.4 medium. These results indicate that the higher swelling ratios of the hydrogel create larger surface areas to diffuse the drug. In basic solutions (pH 7.4), the electrostatic repulsion between COO^- anions of poly (sodium acrylate) on the hydrogel accelerates the release of amphetamine from the hydrogel.

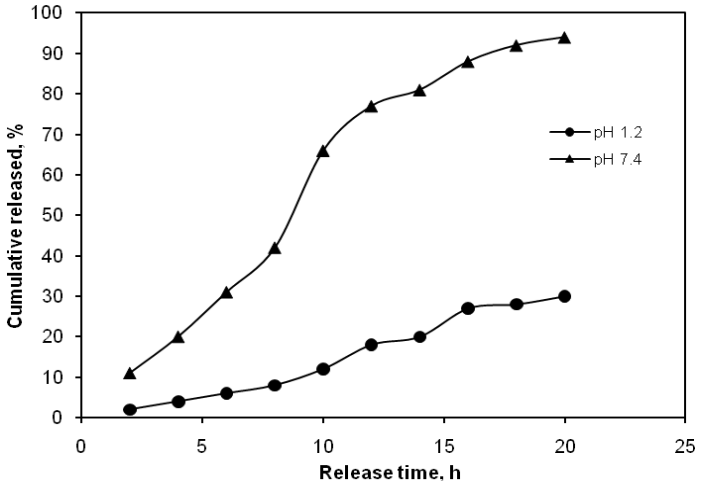


Fig. 3: Release of amphetamine from hydrogel carrier as a function of time and pH.

Conclusions:

In this paper, we prepared IPN hydrogels composed of chitosan and poly(acrylic acid) by crosslinking with formaldehyde. The effect of formaldehyde concentration showed that with increasing of this parameter, the water absorbency of the IPN hydrogels are decreased. The swelling of hydrogels in solutions with various pHs also exhibited a high sensitivity to pH. The release value of amphetamine from hydrogels at pH 7.4 was higher than that at pH 1.2 due to the electrostatic repulsion between carboxylate groups. In general, the IPN hydrogels presented in this study may serve as a platform for a wide range of pharmaceutical uses to improve the bioavailability of non-steroidal anti inflammatory drugs.

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