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Novel Interpenetrating Polymer Network Based on Chitosan for the Controlled Release of Cis-Platin

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ABSTRACT

In the present work, a novel interpenetrating polymer network (IPN) hydrogel composed of crosslinked chitosan and poly(acryl acid) was prepared by crosslinking using glutaraldehyde. The model drug, cis-platin, was loaded into the resulted IPN hydrogel. Water absorption of the hydrogel could be switched on and off swiftly by control of pH of the surrounding environment. Therefore, the synthesized hydrogels in this work can be used as a drug delivery system, and that the drug release can be controlled by the pH of solution. The release rate of cis-platin from hydrogel at pH 7.4 was higher than that at pH 1.2 due to the increased swelling capacity of the hydrogel.
KEYWORDS: hydrogel, acrylamide, chitosan, drug, glutaraldehyde.

1. INTRODUCTION

Hydrogels are the crosslinked hydrophilic polymer networks that are capable of imbibing large amount of water or biological fluids, yet are insoluble in water, but are swollen when immersed [1]. Their water retaining capacity and good biocompatibility makes them important materials in pharmaceutical and biomedical applications [2-4]. Controlled or sustained release drugs provide many advantages in comparison with conventional forms including reduced side effects, drug concentration kept at effective levels in plasma, improved utilization of drug and decrease the dosing times [5]. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving a high drug loading for the required blood levels, immune to accidental release, simple to apply, and easy to fabricate [6, 7].

Recently, studies [8, 9] 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. Among these methods, considerable interest has been devoted to the development of interpenetrating polymer network (IPN) hydrogels [10, 11] 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 [12]. If only one component of the assem- bly is crosslinked leaving the other in a linear form, the system is termed as semi-IPN. Materials formed from IPNs share the properties that are characteristic of each network [13].

Chitosan, a natural poly(aminosaccharide), is non-toxic and easily bioadsorbable. This biopolymer is a weak base with an intrinsic pKa of 6.5 and with gel forming ability at low pH. In acidic solutions, the amine groups of a crosslinked chitosan are protonated and form a cationic hydrogel and result in swelling of the hydrogel network.

The present study is aimed at developing novel type of IPN hydrogels of chitosan with poly(acrylamide) for the controlled release of cis-platin drug. Cis-platin (Fig. 1) is an antibiotic used to treat infections caused by many different types of bacteria. The swelling properties and *in vitro* drug release characteristics of IPN hydrogels have been investigated.

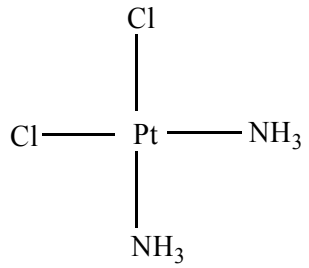

Figure 1. Chemical structure of cis-platin.

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2. Experimental

2.1 Preparation of Hydrogel

Chitosan and IPN hydrogels containing cis-platin were prepared by solution crosslinking. Chitosan and poly(acrylamide) (total polymer concentration of 2%, w/v) were dissolved in 2% aqueous acetic acid solution and stirred overnight to get uniform bubble free solution. Cis-platin equivalent to 30% (w/w) of dry weight of the polymer was added to the above polymer solution and stirred at 400 rpm until a homogenous solution was formed. Then, a mixture of different quantities of glutaraldehyde (GA) and 1mL of 5N HCl was added slowly and stirring was continued for 2h. The formation of IPN structure is schematically shown in Fig. 2.

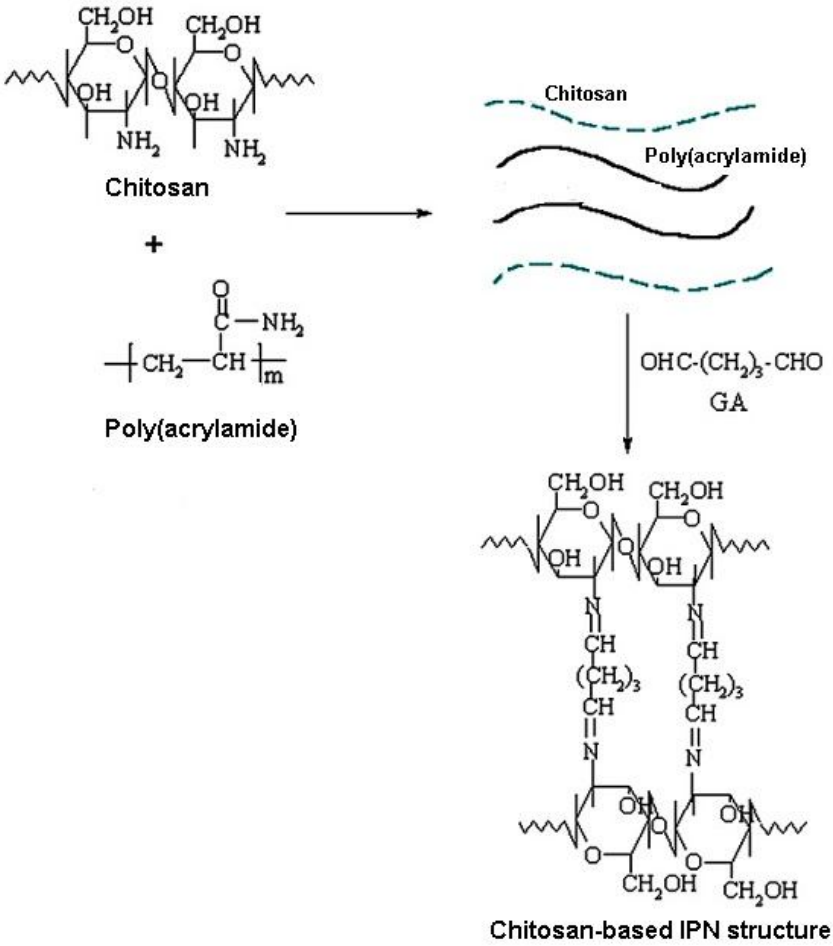

Figure 2. Schematic representation of the formation of IPN structure.

2. 2 pH-sensitivity

IPN hydrogel (0.25 g) were immersed in 250 mL solution with various pH values (pH 1.2 and pH 7.4) at 37 °C to reach swelling equilibrium. Swollen samples were then separated from unabsorbed water by filtering through a 100-mesh screen under gravity for 30 min without blotting the samples. The equilibrium swelling (ES) capacity in buffer solution was calculated according to the following equation:

$$ES(g/g) = \frac{Weight\ of\ swollen\ gel - Weight\ of\ dried\ gel}{Weight\ of\ dried\ gel} \quad (1)$$

2. 3 *In vitro* drug release of IPN

The release of cis-platin was followed as a function of time by measuring the light-absorbance of the outer aqueous phase at 256 nm using an UV/VIS spectrometer 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 using a magnetic stirrer. The same volume of fresh release medium was used to replace what was removed.

3. RESULTS AND DISCUSSION

3. 1 pH-responsiveness behavior of IPN hydrogel

It is known that the pH environment of the gastrointestinal tract varies from acidic in the stomach to slightly alkaline in the intestine. Thus, as an oral drug carrier, pH-sensitivity of IPN hydrogels is a highly significant parameter controlling oral drug release behavior. Thus, pH-sensitivity of the hydrogel is studied as shown in Fig. 3. In order to simulate the possible effect of pH on drug release rate, a swelling study was conducted in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) at physiological temperature of 37 °C. At pH 1.2, the hydrogel swells due to protonation of the amin groups and the resulted repulsive electrostatic forces, while at pH 1.2, it shrinks within a few minutes due to deprotonation of the amin groups. This swelling-deswelling behavior of the hydrogels makes them as suitable candidate for designing drug delivery systems.

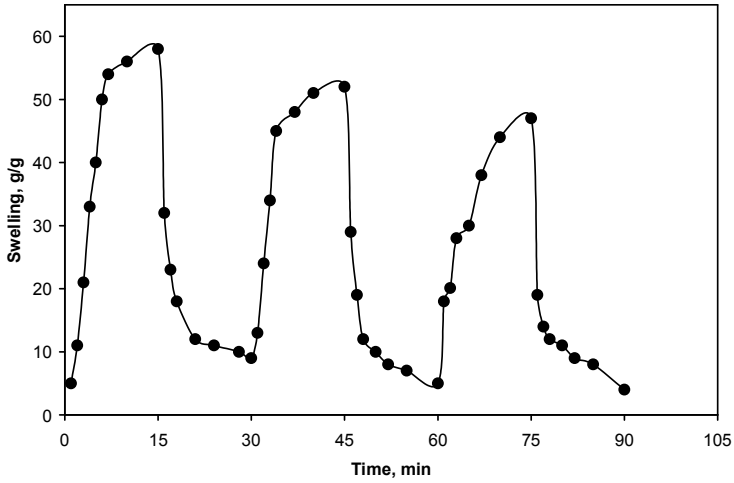

Figure 3. On-off switching behavior as reversible pulsatile swelling (pH 1.2) and deswelling (pH 7.4) of IPN.

3. 2 *In vitro* release behavior of IPN hydrogels

In order to determine the potential application of chitosan-based IPNs containing a pharmaceutically active compound, we have investigated the drug release behavior form this system under physiological conditions. The percent of released drug from the polymeric carriers as a function of time and pH of solution is shown in Figure 4. The concentration of cis-platin released at selected time intervals was determined by UV spectrophotometer. As can be seen from Fig. 4, when pH of the medium is 7.4, the cumulative release ratio of drug from the test hydrogels is below 30% at the end of the experiment (24h), whereas almost 90% of the loaded drug is released within 15h in pH 1.2 medium. This difference of their swelling behavior is responsible for the difference of the drug release ratio with changing pH of the medium. Indeed, the drug in the hydrogel could be released as a result of the hydrogel volume change and interaction between the polymer network and drug. The fractional release is directly proportional to the swelling ratio of the hydrogels.

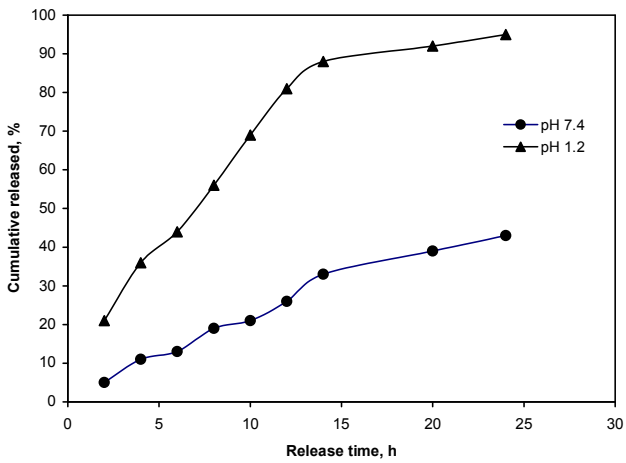

Figure 4. Release of cis-platin from hydrogel carrier as a function of time and pH at 37°C.

5. Conclusion

The reversible swelling-deswelling behavior of chitosan-based IPNs synthesized in this work in solutions with acidic and basic pH makes the hydrogels a suitable candidate for controlled drug delivery systems. It was observed that the release of cis-platin was much higher in SGF compared to SIF, indicating that the release system is controllable and can be as a release system for intestine specific drug delivery. 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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