Synthesis and Characterization of pH-Sensitive Full-Interpenetrating Polymer Networks of Chitosan and Polyacrylic Acid

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ABSTRACT
Biocompatible and biodegradable pH-responsive hydrogels based on polyacrylic acid (PAA) and Chitosan (CS) were prepared by free-radical polymerization in solution. These hydrogels were synthesized using Glutaraldehyde (GA) as a crosslinker for chitosan and N, N’ methylene bisacrylamide (Bis) as a crosslinker for acrylic acid. The swelling kinetics was investigated with changing composition of acrylic acid and crosslinker concentration in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Swelling studies show that the swelling capacity of hydrogels decreased with increasing nominal crosslinking ratio. FTIR studies were performed on hydrogel films to identify functional groups present and interactions in the polymers. The drug, Metronidazole was loaded into these hydrogels, and release studies were carried out in pH 1.2. The release profiles of the drug showed that the drug was released within 15 minutes, and the rest had been released slowly.

Keywords-- Polyacrylic Acid, Polymer, Synthesis

I. INTRODUCTION

Hydrogels are three-dimensional polymeric frameworks that can absorb vast quantities of water or biological fluids[1]. These polymeric hydrogels are made from a small number of synthetic polymers and compounds, including methacrylic acid, acrylamide, and N-isopropyl acrylamide copolymers. In their swelled condition or in actively swelling systems, hydrogels are effective carriers for the distribution of medicines and bioactive macromolecules [2-8]. Their limitation (poor mechanical strength) can be remedied either through crosslinking or through information from interpenetrating networks or by crystallisation, which results in the development of crystallites and a significant reinforcing of their structure.

Cationic character and high charge density have made chitosan a good carrier in oral medication. Chitosan has been extensively studied as a potential carrier for pharmaceuticals taken orally. Furthermore, because chitosan has high mucoadhesive qualities, lengthening the residence duration of drug carriers at the absorption site can result in prolonged release and enhanced bioavailability of pharmaceuticals. Chitosan is a 1,4-linked 2-amino-2-deoxy-D-glucan that is formed when chitin is N-deacetylated [9-11]. Chitosan contains both reactive amino and hydroxyl groups, which can be exploited to chemically change its characteristics under mild reaction conditions. Polyacrylamide is a water-soluble polymer that has a hydrophilic side group and a hydrophobic main chain. Polyacrylamide is a well-known hydrogel with a swelling property that isn't affected by pH or the presence of electrolytes. Amide functional groups have the advantage of being able to inject the needed ionic functionalities into the gel [24].

One of the most appealing applications of the drug delivery system is the release of bioactive compounds from polymeric materials at a specific location. There are, however, numerous obstacles to overcome. The bioavailability of these drugs after oral administration is usually fairly poor since the molecules breakdown in the gastrointestinal system and a considerable portion of the amount absorbed is removed and metabolised by the liver. In some of these uses, the gel's swelling properties are critical, which the chemical structure of the gels may considerably affect [13-14].

The present work aims at the preparation and characterization of pH-sensitive CS/PAAc full-IPNs. Glutaraldehyde as crosslinker for chitosan and N, N’ methylene bisacrylamide (Bis) as crosslinker for acrylic acid was used to form IPNs. The effect of crosslinker concentration (glutaraldehyde, N, N’ methylene bisacrylamide) and blend ratio CS/PAAc on swelling behavior has been investigated in simulated gastric fluid (SGF) of pH 3 and simulated intestinal fluid (SIF) of pH 7.4. Swelling data has been used to characterize hydrogels.
by the number average molecular weight between crosslinks.

II. EXPERIMENTAL METHODS

2.1. Materials

Chitosan, high viscous (CS), was procured from Fluka Biochemika. Acrylic Acid (AAc) monomer was purchased from CDH. Glutaraldehyde as crosslinker for chitosan was purchased from Lobia Chemie Ltd. N, N’ methylene bisacrylamide as crosslinker for acrylic acid was purchased from Merck Pvt. Ltd. Metronidazole (Mz) was a gift from Eaton Lab, Srinagar, India. Glutaraldehyde (25% solution), citric acid, disodium dihydrogen phosphate, potassium chloride, and all other chemicals were analytical grade, and double-distilled water (DW) was used throughout the study.

2.2. Synthesis of Films

Chitosan solutions of concentration 2% (w/v) were prepared in 1% (v/v) acetic acid. The required amount of glutaraldehyde was added to the CS solution and cast on a Petri dish, allowed to air dry at room temperature, and then vacuum dried at 40ºC for 8 h and stored in a desiccator till further use.

CS/AAc films were cast from 2%(w/v) solution. 2%(w/v) AAc solution in distilled water was added in the desired amount to 2%(w/v) CS solution. The required amount of glutaraldehyde was added to CS/AAc solution, and films were cast as described above. Drug-loaded CS/PAAc films were prepared by the addition of Metronidazole to the CS/PAAc solution.

2.3. Swelling Studies

The swelling capacities of CS and CS/PAAc full-IPN films were determined by immersing a 1cm×1cm sample in swelling media at 37±0.1°C. Samples were taken out from each media at regular intervals, blotted with a filter paper to remove the superficial water on the surface, weighed immediately on an electronic balance (Sartorius) within ±0.1 mg, and immersed in the same medium again. The process was continued till equilibrium was attained. The percentage swelling at any time ‘t’ and percentage equilibrium swelling of CS and CS/PAAc films in the media [12] were then calculated by the formula:

\[
\% \text{Swelling} = \left( \frac{W_t - W_d}{W_d} \right) \times 100
\]

Where \(W_t\) = Weight of swelled film

\(W_d\) = Weight of dried sample

2.4. Molecular Weight Between Crosslinks

\[
\left( \frac{1}{M_c} \right) = \left( \frac{1}{M_n} \right) - \left( \frac{\nu}{V_1} \right) \left[ \ln(1 - \nu_{2,5}) + \nu_{2,5} + \chi \nu_{2,5}^2 \right]
\]

\[
\nu_{2,5}^{1/3} - 0.5 \nu_{2,5}
\]

Formula

where, \(M_n\) is the molecular weight of the polymer chains prepared under identical conditions but in the absence of the cross-linking agent,

\(\nu\) is the specific volume of the polymer and

\(V_1\) is the molar volume of water

\(\nu_{2,5}\) is the polymer volume fraction in the swollen state

\(M_c\) is the number average molecular weight between the crosslinks

\(\chi\) is the Flory-Huggins polymer-solvent interaction parameter and its value is 0.5.

2.5. Drug Release studies

Metronidazole is a common antibiotic clinically used to eradicate H. pylori infection, which is considered the main pathogenic factor in developing peptic ulcer disease. The drug release experiments were carried out in SGF (pH 1.2) at 37ºC. Samples were immersed in the medium, and the amount of drug released was followed periodically using spectrophotometer UV-2450 (Shimadzu) at \(\lambda_{max} = 277\) nm.

2.6. FTIR Studies

Infrared Spectra of hydrogels was done by FTIR using a spectrophotometer (Bruker, model Tensor 27).
Transmission spectra in the region of 4000-500 cm\(^{-1}\) were captured at a resolution of 4 cm\(^{-1}\).

III. RESULTS AND DISCUSSION

3.1. Effect of both Crosslinkers and PAAc on Swelling Behavior of CS/PAAc IPNs

Average Molecular weight between crosslinks and polymer volume fraction were considered for characterisation of CS/PAAc IPNs. It was observed that although cross-linked CS films and CS/PAAc full IPNs exhibited considerable swelling in solvent but remained insoluble in solvent. This insolubility of IPNs is due to the formation of imine linkage between the amino group of CS and the aldehyde groups of glutaraldehyde. In contrast to crosslinked films, uncrosslinked films did not swell and they disintegrated after some time. The IPNs were observed to reach equilibrium in almost 3 h. The swelling was significantly higher at pH 3 than at pH 7.4. Since chitosan is a cationic polysaccharide (pKa = 6.3), protonation of the amine group in chitosan takes place in the acidic medium at pH < 6.3 (NH\(_2\) becomes NH\(_3^+\)). The lower the pH of the swelling medium, the higher is the protonation of chitosan, leading to increased electrostatic repulsion of the ionic charges of its network, thus causing a considerable increase in % equilibrium swelling.

The increase in GA concentration causes the decrease in %ES due to an increase in crosslink density of IPNs. This leads to decrease in Swelling capacity of films. It also hinders mobility of polymer chains. It can be seen that % ES reaches a constant value with an increase in GA concentration. The crosslinker concentration was fixed at 25% (v/w) for preparing IPNs.

At pH 7.4 and pH 3, the percent ES drops as the amount of Bis in blends increases while maintaining GA constant. IPNs have a polyelectrolyte complex structure made up of chitosan and PAAc, and the degree of complexation should affect the percent ES of IPNs. In our chitosan/PAA IPN, we could evaluate the two influences on swelling. They have a hydrophilic nature. Polymer hydrophilic groups cause swelling. The hydrophilic group was caught by the polyelectrolyte complex formed between chitosan and PAAc, resulting in a tight and ionic bound structure.

It is also observed that as the amount of AAc increases, %ES of Ch/AAc at pH 7.4 increases, and at pH 3, it decreases. Swelling is due to the ionization of AAc at pH 7.4 as the pKa value of chitosan is 6.5 and that of AAc is 4. AAc exists as COO\(^-\) and Ch exists as ammonium salt in pH 7.4. Ch exist as NH\(_4^+\) salt, and AAc exist as COOH salt.

![Equilibrium %swelling vs. GA(pH 7.4)](image)

**Figure 1:** Effect of amount of GA on %swelling of pure chitosan at pH 7.4
**Figure 2:** Effect of amount of GA on % Equilibrium swelling of pure chitosan at pH 3

**Figure 3:** Effect of amount of Bis on % swelling of Ch/AAc at pH 7.4
Figure 4: Effect of amount of Bis on %swelling of Ch/AAc at pH 3.0

Figure 5: Effect of amount of AAc on %Equilibrium swelling of Ch/AAc at pH 7.4 and pH 3.0

3.2. Drug Release

Figure 6 shows the Drug release from CS/PAAc IPN films at 37±0.1°C in SGF of pH 1.2. The release curves show the fast rate of drug release (within 30 min). It was also observed that as the amount of PAAc increased in the IPNs, the amount of drug released also increased.
These results support the observations of the swelling behavior that increase in PAAc content of semi-IPNs leads to increased swelling because of increased hydrophilicity. This increased swelling causes a higher amount of drugs to be released. Blank runs for films were conducted, which indicated that there was no interaction between constituents of films and buffers.

![Figure 6: Fractional release (cumulative) from CS/PAAc IPNs at pH 1.2](image)

### 3.3. FTIR Analysis

The N-H and O-H stretching bands of chitosan are allocated to a wide peak in the 3200-3700 cm\(^{-1}\) area of the FTIR spectrum. The absorption bands of pure chitosan are 1658 cm\(^{-1}\) (amide I), 1595 cm\(^{-1}\) (amide II), and 1314 cm\(^{-1}\), respectively (amide III). The saccharide structure has absorption bands at 1154 cm\(^{-1}\) (antisymmetric stretching of the C-O-C bridge), 1082 cm\(^{-1}\), and 1032 cm\(^{-1}\) (skeletal vibrations involving C-O stretching).

The presence of the amide II band is the coupled vibration of N-H in-plane bending and amide C-N stretching vibrations. The broad peaks appearing in the range of 2940-2945 cm\(^{-1}\) and 2140-2143 cm\(^{-1}\) confirmed the presence of NH\(_3^+\) in Ch/AAc hydrogels. Asymmetric and symmetric stretching vibrations of COO\(^-\) anion groups could be assigned to the absorption peaks in the ranges of 1562-1570 cm\(^{-1}\) and 1400-1414 cm\(^{-1}\). These findings suggest that the carboxylic groups of PAAc are dissolved into COO\(^-\), which then form a polyelectrolyte complex with protonated amino groups of chitosan via electrostatic contact. With an increase in PAAc concentration in IPNs, the peak appears to move to a lower wavenumber.

**FTIR of pure Chitosan**

![Figure 6: FTIR of CS/PAAc IPNS](image)
IV. CONCLUSION

CS/PAAc IPN films showed higher equilibrium swelling in SGF (pH 1.2) than in other media. The equilibrium swelling increased with the PAAc content of chitosan, but it decreased with an increase in BIS concentration. The results also indicate that metronidazole is adsorbed at the surface as most of the drug is released within 30 min. The results suggest that swelling capacity and the release rate can be controlled by the PAAc content and the crosslinking density. Such films might be helpful for antibiotic delivery in an acidic environment.

REFERENCES