Chitosan-Graft-Polyacrylamide Based Release Systems: Effect of pH and Crosslinking

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Abstract: This study covers the synthesis and release behavior of chitosan-graft-polyacrylamide copolymers in aqueous media at different pH values. The copolymers were synthesized using redox polymerization with ceric ammonium nitrate (CAN) in 1% aqueous acetic acid solution as the initiator. Optimum condition for the graft copolymer synthesis was determined as 3.85 g/L chitosan, 0.27 M acrylamide (AAm) monomer at 40 °C with a CAN per gram chitosan as 6 mmol using 0.05 M stock solution in 0.1 N HNO_3. Then the crosslinked copolymers were synthesized using methylenebisacrylamide (MBA) as a crosslinker varying mass proportions of AAm:MBA as 15:1, 20:1, and 30:1. Obtained material amount (polymer yield) and molecular weight of crosslinked copolymers were lower than the graft copolymer as expected. Acetylsalicylic acid (ASA) release behaviors of all copolymers were monitored with UV-visible spectroscopy at different pH values (2, 6, and 8.5) corresponding to different media in the body (stomach, skin, and intestine, respectively). According to the results, the release behavior changed the least among the samples with respect to medium pH and of was the most affected.

INTRODUCTION

Chitosan is the second most abundant macromolecule in nature after cellulose. It has many aspects being biocompatible, biodegradable, non-toxic, convenient to modification, etc (1,2). It has a linear structure which is composed of 1,4-β-2-amino-2-deoxy-D-glucose (deacetylated D-glucosamine) and N-acetyl-D-glucosamine units. Chitosan is obtained by deacetylation of chitin; in fact, chitin and chitosan are only different in degree of deacetylation (DDA); when DDA is higher than 50% the biopolymer is called as chitosan, otherwise as chitin. The structural features such as crystallinity and solubility are also very closely related with DDA, i.e. chitin and chitosan portions of the 50% DDA biopolymer form an amorphous block copolymer while 99% DDA is a linear, random

semicrystalline copolymer (3). Solubility also increases with increasing DDA; amine groups of the chitosan has a pK value of approximately 6.5 indicating that if the medium pH < 4 chitosan is soluble forming a polycationic structure (3–5).

Ceric ion initiated polymerizations are widely used for aqueous grafting vinyl polymers onto reducing agents which has one or more O-H groups (6), i.e. PEG (7), cellulose (8,9), and xylan (10). Initiation step involves oxidation of O-H groups through a radical pathway. First, ceric ion and reducing agent (i.e. cellulose) form a 5-membered chelate complex; then in acidic medium this complex decomposes, creating a radical on either carbon or oxygen, reducing Ce(IV) to Ce(III) (9). The creation of radicals is a set of complex equilibria including the concentrations of components, temperature and

duration of the reaction. If these factors are not set properly reaction may lead to oxidation of reducing compound terminating the radical created (i.e. low polymer yield). Another problem may be self-creation of radical from air oxygen or from solvent (water) leading to homopolymers. In order to prevent the mentioned side effects an optimum condition has to be found. Having active sites chitosan also can react with ceric ion like cellulose and other polysaccharides (11,12).

Controlled release systems or controlled drug delivery systems are used for delivering some therapeutic agent at a certain site or releasing it slowly in the body; thus the agent is needed to incorporate to a polymeric network structure (13). Chitosan is widely preferred for controlled release systems especially due to unique properties which are mentioned above including biocompatibility and swelling behavior at low pH (1,13). After modification with polyacrylamide swelling property of chitosan enhances and this copolymer may be used as a matrix which become very popular component for controlled release systems. There are many parameters affecting swelling, and in turn release behavior, of the copolymer; some of these parameters are pH, temperature, concentration, and salinity (2,14,15). Chitosan-polyacrylamide release matrix is used in earlier studies with several differences, for example Bulut has used chitosan-graft-polyacrylamide matrix supporting with carboxymethylcellulose to encapsulate and release ibuprofen (12), and Wang et al. has grafted polyacrylamide and poly(N-isopropylacrylamide) to chitosan to use obtain a gel structure both sensitive to pH and temperature (16). Presence or number of crosslinks among the copolymer which is grafted onto chitosan chains may affect the release rate in media with different pH values.

In this study, chitosan functionalization via redox polymerization using ceric ammonium nitrate as initiator to graft linear or crosslinked polyacrylamide moieties onto chitosan has aimed in order to obtain controlled release systems. First, optimization of the reaction conditions was achieved. Then spectral and physical characterizations of the samples was done. Finally, controlled release experiments were done at different pH values which were corresponding to different environmental values as acidic (pH 2, stomach), nearly neutral (pH 6, skin), and basic (pH 8.5, intestine).

MATERIALS AND METHODS

Chemicals and solutions
Chitosan 99% DDA (Sigma Aldrich), nitric acid (65%, d=1.40 g/mL, Merck), acrylamide (AAm) (Merck), methylenebisacrylamide (MBA) (Fluka), sodium hydroxide (Merck), acetylsalicylic acid (ASA) (Sigma-Aldrich), glacial acetic acid (Merck), isopropyl alcohol (technical grade, distilled prior to

every use), acetone (Merck). Rest of the chemicals were all of Merck brand and used as received.

Ceric ammonium nitrate (CAN) was Sigma-Aldrich brand and it was used as a stock solution of 0.05 M in 0.1 M nitric acid.

Acidic buffer solution (pH 2) was prepared dissolving KCl (7.45 g) in water; then HCl (37%, 1.75 mL) was added to the mixture and completed to 1.0 L with distilled water.

Slightly acidic buffer solution (pH 6) was prepared dissolving $Na_2HPO_4 \cdot 7 H_2O$ (1.307 g) and $NaH_2PO_4 \cdot H_2O$ (13.127 g) in water; then the mixture completed up to 1.0 L with distilled water.

Basic buffer solution (pH 8.5) was prepared dissolving H_3BO_3 (61.83 g) and NaOH (10.00 g) in water; then the mixture completed to 1.0 L with distilled water.

Instruments
FTIR measurements were carried out on Thermo Scientific Nicolet 380 equipped with a diamond crystal ATR module in a range of 4000–400 cm^{-1} in percent transmission mode.

NMR measurements were carried out on an Agilent instrument (500 MHz for ^1H, 11.7 T) using D_2O as solvent.

UV-visible spectra were taken on Perkin Elmer Lambda 25 model instrument in 200-400 nm wavelength range.

Molecular weight determination
Molecular weight determinations were carried out using viscometric method with Ubbelohde viscometer. Mark-Houwink constants for polyacrylamide was $K = 6.31 \times 10^{-3}$ mL/g and $a = 0.80$ in water at 30 °C. (17) Intrinsic viscosity ($[\eta]$) was determined using Solomon-Ciuta equation (1). (18,19)

$$[\eta] = \frac{\sqrt{2 - (\eta_{sp} - \ln \eta_{rel})}}{C} \qquad (1)$$

Thermogravimetric analyses
Thermogravimetric analyses (TGA) were carried out on a Perkin Elmer Pyris 1 TGA with a heating rate of 20 °C/min in 30-1000 °C range.

Statistical analysis
Principal component analysis (PCA) was performed on first derivative FTIR data using R software (version 4.0.0) running on 64-bit MS Windows 10 platform. First order derivatives of the spectra in range between 1800 and 850 cm^{-1}, which were calculated via the Savitzky-Golay algorithm averaging 4 points left and right side using a third

order polynomial, were used in order to eliminate the errors that could arise from overlapping.

Synthesis of Chitosan-graft-Poly(Acrylamide) (ChAAm)

Chitosan (0.1 g) and AAm (0.5 g) were dissolved in 10 mL 1% acetic acid separately in 15 minutes at 40 °C; then both solutions were mixed to have a chitosan:AAm mass proportion of 1:5. After stirring at 40 °C for another 15 minutes 6 mL of CAN solution was slowly added to the mixture in 15 minutes. Polymerization was allowed to continue for 3 hours at the same temperature. Then the mixture was poured into 5 volumes of isopropanol to precipitate grafted copolymer. The medium pH was adjusted with to approximately 9 with 1 M NaOH; then the alcoholic mixture was left to precipitate the small chains overnight at -35 °C. The graft copolymer was separated centrifuging at 200-G for 5 minutes, then left to dry first in air, then in the vacuum.

The percentage (G%) and efficiency (E%) of grafting was calculated as following equations (2) and (3). (11)

$$G\% = \frac{W_{cop} - W_{chitosan}}{W_{chitosan}} \times 100 \qquad (2)$$

$$E\% = \frac{W_{cop} - W_{chitosan}}{W_{monomer}} \times 100 \qquad (3)$$

Synthesis of Crosslinked Grafted Copolymer (ChAAx)

Polymerization procedure for crosslinked copolymers was similar, but after addition of CAN solution methylenebisacrylamide (MBA) was added to the mixture as crosslinking agent in different proportions relative to AAm. The proportions of AAm:MBA were 15:1, 20:1, 30:1, by mass. The

termination and precipitation parts of the procedure was followed likewise.

Loading and Releasing Acetyl Salicylic Acid

Loading of ASA was carried out using polyelectrolyte complex (PEC) method. The copolymer (108 mg) was dissolved in 10 mL of 1% acetic acid; in another container acetylsalicylic acid (ASA) was dissolved in 10 mL of water, then it was made alkaline with addition of 1 M NaOH. The alkaline ASA solution was dripped slowly into acidic copolymer solution in 10 minutes. Afterwards, the ASA-copolymer mixture was poured into acetone solution to precipitate. In order to accelerate and promote precipitation the final solution was cooled in deep freeze (-25 °C). The loaded copolymers were collected centrifuging the cold mixture. The loaded samples were washed with acetone, dried first in air, then in vacuum. Then the loaded copolymer was pressed to convert into a pellet.

Release of ASA from the copolymer matrix was monitored using UV-visible spectroscopy using the intensity of the signal located at 300 nm. First calibration curves were obtained for ASA at 3 different pH using proper buffer solutions. Then the loaded copolymer was placed in a container with 10 mL appropriate buffer solution and UV measurements were done periodically.

RESULTS AND DISCUSSIONS

Chitosan is a naturally occurring polymer and is mainly composed of β-2-amino-anhydroglucose units linked through 1 to 4 positions. Having active OH sites chitosan reduces ceric ion, creating radicals with a redox reaction leading to initiation of a vinyl polymerization (6). Radical generation from cellulose is related with a chelate complex formation (8,9). Thus a similar path is expected for chitosan; the formed radical may be on nitrogen, oxygen, or carbon (Figure 1).
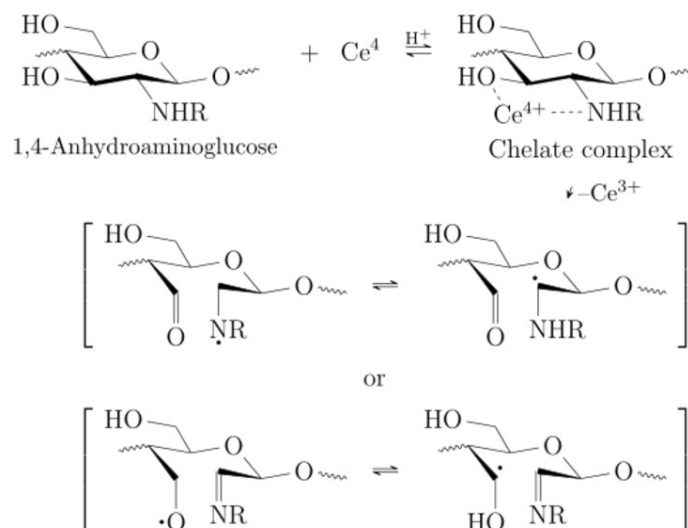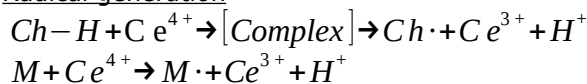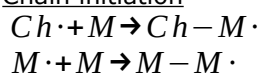
Figure 1: Plausible mechanism of radical generation with ceric ion and chitosan.

Although a reducing agent is needed to create radicals, sometimes ceric ion and aerial oxygen (or water) can also react to produce radicals, leading to homopolymers. The possible reactions were given in the scheme below. This unfavorable situation can be prevented adjusting reaction conditions. Other unwanted side reactions involving reducing agent, chitosan, were degradation in acidic medium or oxidation by ceric ion.
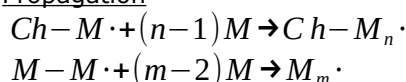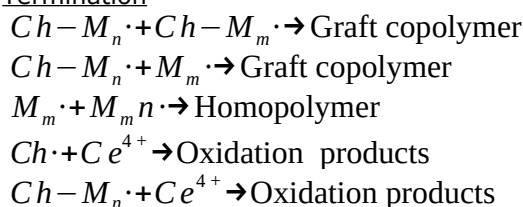
Radical generation

$$Ch-H + Ce^{4+} \rightarrow [Complex] \rightarrow Ch\cdot + Ce^{3+} + H^+$$
$$M + Ce^{4+} \rightarrow M\cdot + Ce^{3+} + H^+$$

Chain initiation

$$Ch\cdot + M \rightarrow Ch-M\cdot$$
$$M\cdot + M \rightarrow M-M\cdot$$

Propagation

$$Ch-M\cdot + (n-1)M \rightarrow Ch-M_n\cdot$$
$$M-M\cdot + (m-2)M \rightarrow M_m\cdot$$

Termination

$$Ch-M_n\cdot + Ch-M_m\cdot \rightarrow \text{Graft copolymer}$$
$$Ch-M_n\cdot + M_m\cdot \rightarrow \text{Graft copolymer}$$
$$M_m\cdot + M_m n\cdot \rightarrow \text{Homopolymer}$$
$$Ch\cdot + Ce^{4+} \rightarrow \text{Oxidation products}$$
$$Ch-M_n\cdot + Ce^{4+} \rightarrow \text{Oxidation products}$$

Scheme 1: Possible reactions in the medium containing chitosan (Ch), CAN (Ce⁴⁺), and monomer (AAm, MBA).

Ceric ion initiated polymerization reactions were affected by several factors including total acid concentration, reducing agent type, concentrations, reaction temperature, and duration (7,20,21). These factors were interfering among each other; thus an optimization run was necessary for different monomer and/or reducing agent couples to have a maximum yield of desired product, i.e. graft copolymer. As previous studies implied each factor had an individual apex interfering with each other starting with a predetermined condition obtained from earlier works was favorable (7,8,10).

Releasing experiments were carried out in 1% acetic acid in order to carry out the reaction in a homogeneous solution as chitosan was soluble in acidic solutions. As the results indicated that using inert atmosphere was not needed. Changes in temperature and/or reaction period caused a decrease in G% and E%. Optimum conditions were determined as 40 °C, 3.85 g/L chitosan, 0.27 M AAm; CAN proportions were used as 6 mmol CAN per gram chitosan, and 43 mmol CAN per mol AAm. Under these conditions a G% of 350% was observed (E% was 70%) and copolymer labelled as ChAAm.

Blank experiment (using the same conditions without chitosan) resulted in a reaction yield of 8%. This result indicated that chitosan was needed to produce radicals to start the polymerization.

After determining optimum conditions crosslinked copolymers were synthesized using same parameters with addition of MBA as crosslinking agent at different amounts. AAm:MBA proportions were set as 15:1, 20:1, and 30:1 by mass; these proportions were corresponding to 33:1, 43:1, and 65:1 AAm:MBA by mole. The crosslinked copolymers were labelled as ChAAx-15, ChAAx-20, and ChAAx-30 after their AAm:MBA proportions. Introduction of MBA resulted in a decrease in obtained product amount in the first place. When a detailed examination was made it was seen that G% was decreasing with an increase in AAm:MBA proportion. As the proportion was adjusted as 15:1,

20:1, and 30:1 the G% values were observed as 317, 206, and 157%, respectively. Also, E% was affected in a similar manner; it was observed as 60, 40, and 31% for ChAAx-15, ChAAx-20, and ChAAx-30 while it was 70% for ChAAm. This occurrence was probably due to crosslinks of MBA were both amongst acrylamide chains and chitosan chains at the same time.

Characterizations of Graft Copolymers

Molecular weight determinations were done utilizing the viscometric method. Intrinsic viscosity, and in turn molecular weight of the copolymers, was determined by Solomon-Ciuta and Mark-Houwink equations, respectively. Mark-Houwink constants (6.31×10^{-3} mL/g and $\alpha = 0.80$) belong to polyacrylamide in aqueous solution at 30 °C (17). Although this method could not give the absolute molecular weight, it might give useful information about the samples for comparitive purposes. The molecular weight of ChAAm was determined as 55 kDa while increasing MBA component caused a decrease; molecular weight of ChAAx-15 was 17

kDa, it was measured as 12 kDa for ChAAx-20 and as 10 kDa for ChAAx-30.

Characteristic FTIR signals that were related to chitosan were summarized as O-H and N-H stretching vibrations (overlapped) as a broad signal with peak positions at 3357 and 3282 cm^{-1}, various C-H stretching vibrations with a peak at 2870 cm^{-1}. Amide I and/or adsorbed water vibrations were observed at 1644 cm^{-1}, amide II vibration at 1566 cm^{-1}, various C-C-H, C-O-C, C-C-O bending, and C-C, C-O stretching vibrations between 1500–800 cm^{-1}. The signal at ca. 899 cm^{-1} belonged to the anomeric (C$_1$) region of the chitosan indicating β conformation (5).

The FTIR spectrum of obtained copolymer (ChAAm) displayed characteristic signals of polyacrylamide besides chitosan; stretching vibrations at 3341 and 3206 cm^{-1}, amide C=O stretching (amide I) at 1660 cm^{-1}, bending (amide II) at 1621 cm^{-1}, stretching (amide III) at 1422 cm^{-1} (22) (Figure 2).
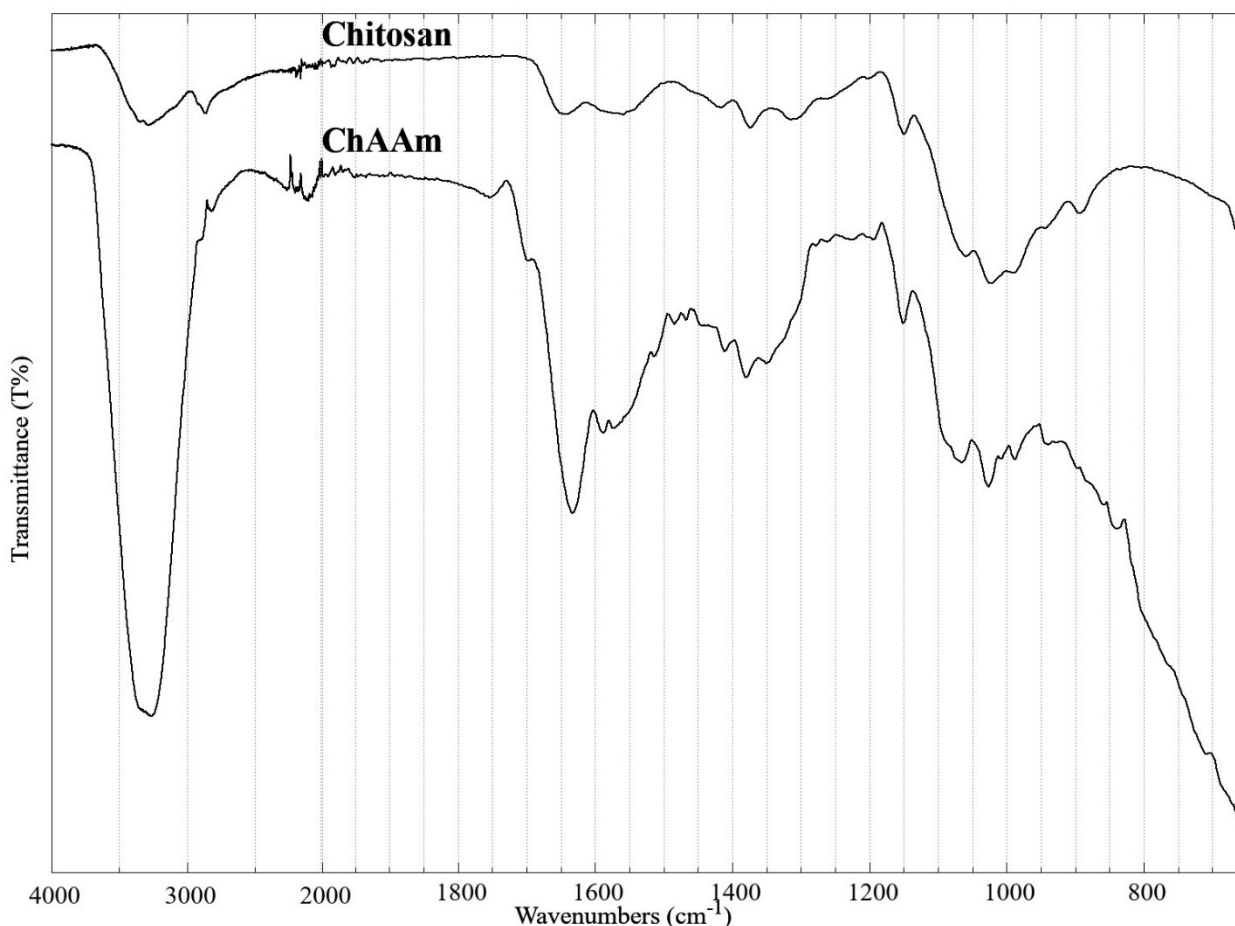

Figure 2: FTIR spectra of chitosan and ChAAm copolymer.

Comparison of FTIR spectra belonging to chitosan and ChAAm indicated that grafting of polyacrylamide onto chitosan was achieved. Crosslinking agent, MBA, caused a broadening in

amide I, and II signals, also an additional signal at amide III region was observed. As these signals appeared with introduction of MBA it was thought that crosslinked copolymers were obtained.

Additionally, C_1 related signal was observed around 895 cm^{-1} for crosslinked copolymer indicating a slight conformational relaxation on chitosan backbone.

FTIR spectra of chitosan and acrylamide copolymers were quite similar in many aspects. Moreover, C=O stretching vibrations of acrylamide moieties overlapped with chitosan signals. In order to identify and characterize copolymers a statistical method, PCA, was applied to the FTIR data. Sampling a typical FTIR spectrum several hundreds of points in correlation to each other stored. Applying PCA this correlation was removed creating uncorrelated variates known as principal component (PC) scores. The PCs could be defined as new, orthogonal axes where variances were maximized. Thus, the projection of PCs against one another could reveal the clustering or structural information regarding

the major components that are responsible for the change in certain region of the spectrum.

The scores plot of the first three PCs, which together account for 99% of total variance, was shown in Figure 3. In the plot PC1 and PC3 were used as x- and y- axes, respectively, same colors indicating near-by groups in PC2. Chitosan appeared nearly at the center of the plot while ChAAm was observed at the right-hand side of PC1. As this occurrence was related with grating a detailed analysis on loadings plot of the PCs indicated that positions on the plot were mainly related with amide C=O stretching vibration (from AAm) around 1670 cm^{-1} and C-O (of chitosan backbone) related signals in 1300-900 cm^{-1} range. Introduction of crosslinking agent resulted in shifts on PC3 while slight changes were observed or PC1. This result also supported that the presence of MBA leads to more crosslinked structures than grafting onto chitosan backbone.
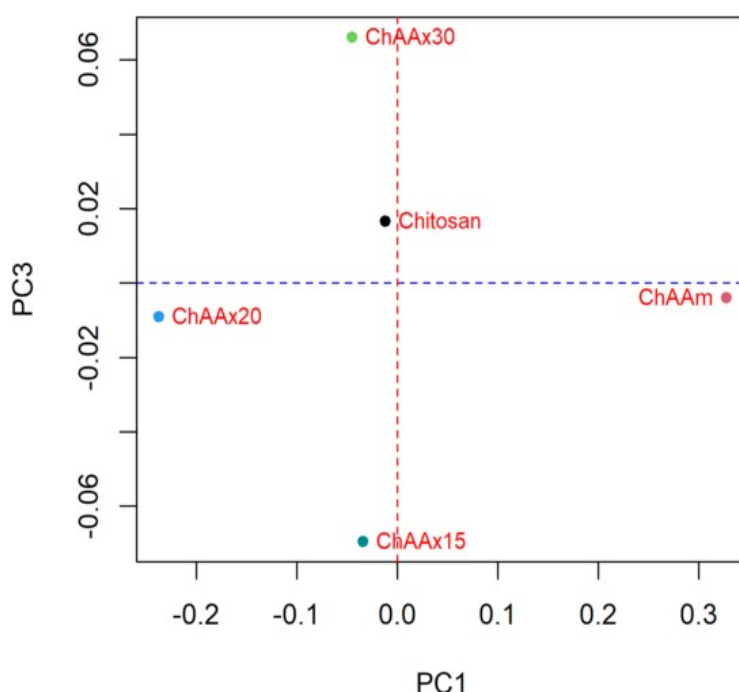

Figure 3: Resulting scores plot of PCA for copolymer samples.

Thermal characterizations of copolymers were carried out using TGA. First loss was due to adsorbed water, and was observed as a broad signal starting around 40 °C and ended around 150 °C with a proportion of 10 to 15%. This loss had a maximum weight loss temperature, T_{H2O}, observed at 101 °C for chitosan. Then another degradation was observed between 250 and 430 °C; the maximum degradation temperature, T_{max}, for this event was also determined from derivative TGA (DTGA) plot as 334 °C.

Introduction of polyacrylamide moiety onto chitosan backbone resulted in an increase in T_{H2O}; it was observed as 125 °C for ChAAm. In addition, an increase in the intensity of derivative peak indicated

that introduction of polyacrylamide moieties increased the water uptake of the copolymer as expected. The second decomposition, which was related, with mainly decomposition of polyacrylamide portion observed between 250 and 400 °C with a peak position at 300 °C in DTGA. There was also an additional signal maximum in DTGA located at 487 °C that was related with the second stage decomposition of polyacrylamide.

Crosslinked copolymers displayed slightly higher values for each thermal event. Water loss signal was observed as 112 °C for ChAAx-15, 130 °C for ChAAx-20, and 93 °C for ChAAx-30. Polyacrylamide decomposition pattern was observed in the same range with ChAAm; however, maximum degradation

temperatures were changing according to AAm:MBA ratio. ChAAx-15 and ChAAx-30 had a small signal around 280 °C and a stronger signal peaked around 310 °C which was very close to the peak signal for ChAAm. However, ChAAx-20 displayed two distinct signals in this range one was located around 330 °C and another at 386 °C. The shape pattern was also different for this decomposition. This occurrence was probably due to different amounts of crosslinking in the structure.

Release Experiments
Controlled release experiments were done using 4 different copolymer matrices (ChAAm, ChAAx-15, ChAAx-20, ChAAx-30) at 3 different pHs (2, 6, and 8.5). Releasing material was acetylsalicylic acid (ASA). The experiments were carried out at ambient temperature; ASA:copolymer proportion were kept

constant at 1:3 by mass. ASA was loaded to the copolymer matrix using polyelectrolyte complex (PEC) method. In this method, ASA was encapsulated by copolymer matrix.

After preparation the pellets were placed in corresponding buffer solutions for pH 2, 6, or 8.5. The pH selection of the buffers was done for imitating the medium of stomach (strongly acidic), skin (weakly acidic or nearly neutral), and intestine (basic) for in vitro studies, respectively. In order to monitor the release of ASA calibration measurements were done separately in corresponding buffer solutions. The collected data was evaluated in two ways: the effect of the crosslinking at the same pH (Figure 4), and the effect of the pH for same matrix (Figure 5).
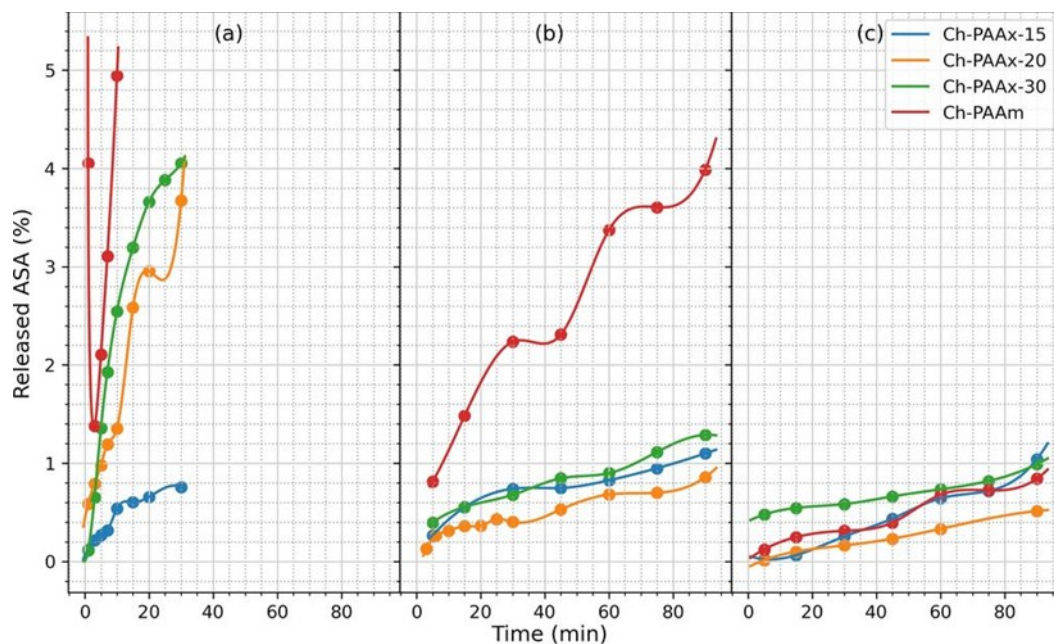

Figure 4: ASA release from the ASA:copolymer matrix at pH a) 2, b) 6, c) 8.5.
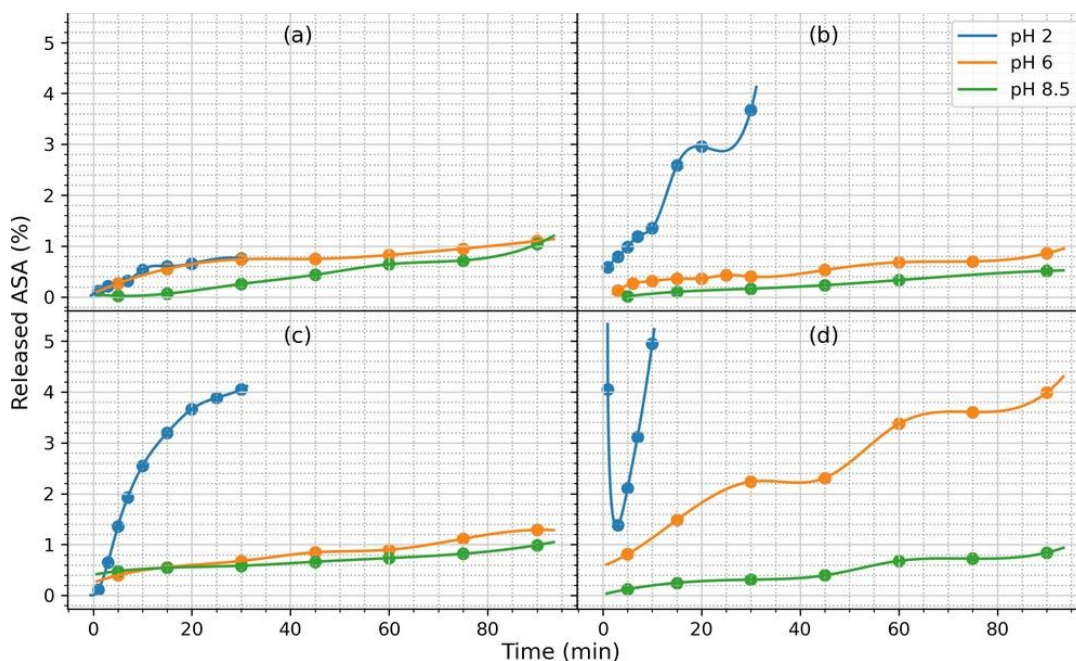
Figure 5: ASA release from the ASA:copolymer matrix based on a) ChAAx-15, b) ChAAx-20, c) ChAAx-30, d) ChAAm.

The UV-visible spectrum of ASA displayed several absorption bands within the wavelength range of 200-450 nm. The strongest signals were located around 200 nm with two peak positions one was located around 215 nm, and the other was at 225 nm. This distinction was clear for pH 2, but for other pH values 225 nm signal lost intensity and became a shoulder to 215 nm. Another strong signal was located at 300 nm. All signals were shifted insignificantly as a result of changing medium pH. Chitosan displayed a signal only around 200 nm due to amide carbonyl transitions especially for pH 2, in the other two spectra this signal was observed slightly lower than 200 nm, so only tailing part of the signal was seen. Thus, quantitative ASA measurements were taken using the signal at 300 nm in order to prevent interferences.

The release rate was influenced by medium acidity as the matrix was very sensitive to pH (Figure 4a-c). Having N-H groups with an approximate pK value of 6.5 (4,5) chitosan backbone was expected to dissolve in acidic media. However, grafted polyacrylamide moieties retarded or prevented complete dissolution possibly due to extensive hydrogen bonding and/or crosslinking resulting in swelled structures. Increasing amount of MBA resulted in a structure with a higher number of crosslinks; thus, swelling behavior was influenced by composition.

For ChAAm, release behavior was extremely different from the rest of the samples at strongly acidic pH. First, a high and rapid UV response was observed when the matrix was placed in release medium; then the response decreased until 1.4% and then increased again. A possible explanation for

this event was fast expansion of the matrix in acidic medium. In this case, hydrogen bonds were the only interaction holding the matrix together; when dissolution occurred in the buffer, the loaded ASA was released at once in an uncontrolled fashion. However, later the dissolved polymer chains readsorbed ASA leading to a decrease in the UV absorption and then release of ASA was started again at a lower rate.

Unlike ChAAm, crosslinked copolymers displayed a more stable release behavior as expected. All crosslinked copolymers displayed a linear model for release, except ChAAm-20 that released ASA displaying a logarithmic model. Among the crosslinked copolymers, the slowest release was observed for ChAAx-15, which had the highest MBA proportion thus the highest number of crosslinks. This was expected, as intensive number of crosslinks caused the smallest pore size of the matrix; thus, ASA was released slower via these pores of the swelled matrix at a small rate. At this pH ChAAx-30 was also displayed a similar behavior indicating even a small number of covalently bonded crosslinks was affecting the swelled structure and its pore size as the matrix did not disperse easily in the medium and standing together forming up a swelled structure. Then ASA should permeate through the pores of this swelled structure. ChAAx-20 and ChAAx-30 displayed similar results with an exception in release model. When compared the release based on the component ChAAx-20 matrix was nearly linear while ChAAx-30 matrix was more a fit to logarithmic model.

When pH was changed to 6.0 release rate slowed down for all copolymers. Still being in a medium

more acidic than pK value of chitosan, ChAAm based matrix displayed the highest release rate among them. The rest of the matrices displayed very close results. All matrices displayed an almost linear release model.

A similar result was also observed for pH 8.5; this time even release from the matrix based on ChAAm was very close to the crosslinked copolymers.

At the same pH the difference in release behavior was due to swelling characteristics; as expected the smaller the pore size or the higher the number of crosslinks the slower the release rate.

In Figure 5a-d release behavior was shown as a function of copolymer composition; the release differences for the same copolymer at different pH values.

When the plots were evaluated, it was seen that pH clearly affected the release rate as well as composition of the copolymer. Amongst the copolymers, the slowest release was observed for ChAAx-15 regardless the medium acidic properties. It was the least affected matrix material due to extensive crosslinks of MBA.

Because of a decrease in MBA amount of the copolymer, corresponding to a decrease in crosslink intensity matrices became more sensitive to the medium pH. ChAAx-20 and ChAAx-30 gave very similar results; they released ASA rapidly in acidic medium while release was slowed down to similar values at higher pH values for both. The most sensitive matrix was ChAAm based; it was affected by medium pH dramatically. As mentioned above it released ASA at once re-adsorbing and re-releasing it again at a slower rate in acidic medium. At pH 6 release rate decreased and became more stable than acidic medium. In basic medium, the release rate decreased down to the lowest rate, which was very close to the rest of the copolymers.

CONCLUSION

ChAAm was synthesized with an efficiency of 68% corresponding to 340% grafting. Using determined condition crosslinked copolymers were synthesized with 15:1, 20:1, 30:1 mass proportions of AAm:MBA (ChAAx-15, ChAAx-20, ChAAx-30, respectively). The expectation was as the AAm:MBA proportion went higher MBA amount went lower resulting in a decrease in crosslinking. The results indicated that change in AAm:MBA proportion lead to different efficiency and grafting percentages. Thus, optimizing studies could be done for higher efficiency values for different proportions and/or a kinetic model would be determined.

The release behaviors of the prepared copolymers were monitored at 3 different pH values as 2, 6, and

8.5 for model media for stomach, skin, and intestine media, respectively. Loading ASA and monitoring release at different pH media indicated that the least pH sensitive matrix among these was ChAAx-15 as it was stable and similar release behavior at all pH values, and the most pH sensitive was ChAAm as it had nothing but hydrogen bonds to hold the matrix together. According to the results, ChAAm based release matrices were suitable for skin-care applications while ChAAx-15 based ones were suitable for all pH values to release at a steady rate. Further studies could be done with different therapeutic agents, at different temperatures, and in vivo tests could be run.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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