Evaluation of the Potential of Polymeric Carriers Based on Chitosan-*grafted*-Polyacrylonitrile in the Formulation of Drug Delivery Systems

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ABSTRACT: Graft copolymerization of chitosan with acrylonitrile (AN) was carried out by free radical polymerization using $KMnO_4$ and oxalic acid as a combined redox initiator system. Graft copolymerization was confirmed by Fourier transform infrared spectra (FTIR), proton nuclear magnetic resonance spectra (^{1}H-NMR), thermal gravimetric analysis (TGA) measurements, and wide angle X-ray diffraction (WAXD). In addition, further modification of the cyano groups of the grafted copolymers was performed by partial hydrolysis into carboxylic function groups with various extents. The extent of hydrolysis was monitored using FTIR spectroscopy. The potential of the hydrolyzed and unhydrolyzed grafted copolymers as polymeric carriers for drug delivery systems was extensively studied by preparation of tablets incorporated with methyl orange (MO) as a drug model. *In vitro* drug release was carried out in simulated gastric and intestinal conditions. The effects of grafting percentage (GP) and the extent of hydrolysis on the release kinetics were evaluated. Release continued up to 24 h for both hydrolyzed and unhydrolysed chitosan-*g*-PAN copolymers. The nature of drug transport through the polymer matrices was studied by comparing with power law or Kormeyer-Peppas equation. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 118: 1837–1845, 2010

Key words: chitosan; acrylonitrile; grafting; drug delivery

INTRODUCTION

Chitosan is a partially deacetylated polymer of acetyl glucosamine obtained after alkaline deacetylation of chitin. It displays interesting properties such as biocompatibility, biodegradability,[1–3] and its degradation products are non-toxic, non-immunogenic, and non-carcinogenic.[4,5] Therefore, chitosan has prospective applications in many fields such as biomedicine, wastewater treatment, functional membranes, and flocculation. Due to its physicochemical and biological properties, the study of chitosan and its derivatives as a carriers for various active agents including drugs and biologics has become a very interesting and active research area in recent years. It is extremely important that chitosan is hydro-soluble and positively charged. These properties enable it to interact with negatively charged polymers, macromolecules, and polyanions on contact in an aqueous environment. It has the special feature of adhering to mucosal surfaces, a fact that makes it a useful polymer for mucosal drug delivery. Chitosan has interesting biopharmaceutical characteristics such as pH sensitivity, biocompatibility, and low toxicity. Moreover, chitosan is metabolized by certain human enzymes, especially lysozyme and is considered biodegradable.[6] However, chitosan is only soluble in few dilute acid solutions, which limits its applications. Recently, there has been a growing interest in chemical modification of chitosan to improve its solubility and widen its applications.[7–9] Among various methods, graft copolymerization is most attractive because it is a useful technique for modifying the chemical and physical properties of natural polymers.

Chitosan bears two types of reactive groups, the free amino group on deacetylated units and the hydroxyl groups at the C_3 and C_6 on acetylated or deacetylated units,[10] which will enable the easy occurrence of graft copolymerization on chitosan. Studies on the graft copolymerization of chitosan with various vinyl monomers have been conducted with different initiating systems and different mechanisms. There are mainly two kinds of initiating systems, chemical initiation and radiation initiation, to graft copolymerize different vinyl monomers such as vinyl acetate, acrylonitrile (AN), methacrylic acid (MA), and methylmethacrylate (MMA),[11,12] onto chitosan. There are reports about graft copolymerization of vinyl monomers onto polysaccharides using both high energy (e.g., γ, β, X-ray) and low energy (e.g., photo, UV light) radiations.[13,14] Although graft copolymerization with radiation initiation offers an economical and quick method, they are harder to handle under technical conditions.[15] Graft copolymer

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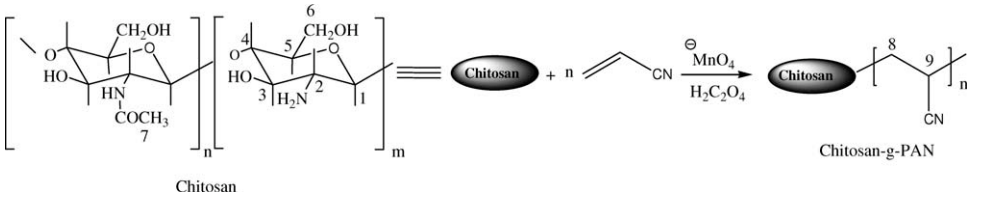


Scheme 1 Synthesis of chitosan-*g*-PAN using $KMnO_4$/oxalic acid combined redox initiator.

of carboxymethyl chitosan with MA was prepared by using the ammonium persulfate as the initiator and the grafted copolymer water solubility was greatly improved.[16] The preparation of chitosan-graft-polyacrylonitrile was carried out in a homogeneous acetic aqueous phase by using ceric ammonium nitrate as an initiator.[17] In another work, graft copolymerization of AN and MMA onto chitosan using potassium persulfate ($K_2S_2O_8$) as an initiator was studied.[18] As a kind of high efficient initiator, the compound of salt persulfate and cerium ammonium nitrate were more investigated compared with the thermal initiator AIBN.[19] Fenton's reagent is another frequently used initiator for graft copolymerizing vinyl monomers onto chitosan, which involves the redox initiating system. Comparative studies of graft copolymerizing MA and MMA monomers onto chitosan using $K_2S_2O_8$ alone and $K_2S_2O_8$ coupled with various co-catalysts ($MnCI_2$ or oxalate) were made, and the effects on the grafting rate were different.[20] $K_2S_2O_8$ alone can initiate the radical reaction with forming a redox pair with the anhydroglucose units of the polysaccharide to yield the macroradicals, which sometimes results in the degradation of chitosan.[21,22]

Of the chemical initiators used for the grafting, the Mn(IV) ion in the presence of an activator has proved to be an efficient initiator.[23,24] The aim of this study was to conduct a kind of chemical modification of chitosan by using the method of graft copolymerization of AN onto the backbone of chitosan using $KMnO_4$/oxalic acid combined redox initiator, the products of chitosan-grafted-polyacrylonitrile were characterized by FTIR, ^{1}H-NMR, thermal gravimetric analysis (TGA), and wide angle X-ray diffraction (WAXD), which elucidated the structure changes in comparison with chitosan, the cyano groups of the copolymers were partially converted to carboxylic acid groups by hydrolysis reaction. Both types of the resulting copolymers were used as carriers for the formulation of drug delivery systems.

MATERIALS AND METHODS

Materials

Chitin was isolated from pink shrimp *(Solenocera melantho)* shell waste by treatment with 2.5 *N* NaOH (12.5 mL/g of shrimp shell powder at 75°C for 6 h) and 1.7 *N* HCl (9 mL/g of shrimp shell powder at ambient temperature for 6 h). Chitosan (M_w 6.5 × 10^5 amu) and degree of deacetylation 85% was prepared by N-heterogeneous deacetylation of chitin in aqueous 50% sodium hydroxide solution under solid–liquid–liquid phase transfer catalytic condition according to our previous study.[25] Briefly, 5 g chitin was soaked overnight in chloroform as swelling medium. After decantation of the solvent, the swollen polymer was treated with 500 mL 50% aqueous NaOH solution and 5.16 × 10^{-3} mol/L of the phase transfer catalyst Benzyltriphenyl phosphonium chloride (BTPP) (BDH) at 50°C. The reaction mixture was mechanically stirred for 6 h. After cooling, the resulted deacetylated chitin was washed by distilled water until alkali free, and then the degree of deacetylation was determined using FTIR spectra as mentioned in our previous work.[25] AN (BDH-England) was treated with 3% sodium hydroxide solution, washed with distilled water until neutralization, dried over calcium chloride followed by molecular sieves. Oxalic acid (Adwic), $KMnO_4$ (BDH-England), and Methyl orange (MO) (Aldrich) were reagent grade. All other chemicals were analytical grade or above and used as received without further purifications.

Synthesis of chitosan-grafted-polyacrylonitrile (chitosan-*g*-PAN)

Chitosan-*g*-PAN was prepared by the reaction of chitosan with AN in presence of oxalic acid and $KMnO_4$ as a combined redox initiator as shown in Scheme 1. The formulation details used in synthetic procedure are summarized in Table I. First, 1.25 g chitosan was dissolved in 25 mL of 2% acetic acid in water (Sol A). Specific amounts of oxalic acid and

TABLE I
Synthesis of Chitosan-*g*-PAN Under Various Conditions[a]

Formulation code	AN (mol/L)	GP (%)
P_1	0.95	70
P_2	1.9	160
P_3	2.8	250

[a] Concentration of chitosan = 25 g/L; $KMnO_4$ = 4.1 × 10^{-2} mol/L and oxalic acid = 8.2 × 10^{-2} mol/L, reaction time was 2 h at 50°C.

$KMnO_4$ were then charged in another vial that contained a 25 mL of water and stirred for 2 min until full dissolution (Sol B). Sol B was then added into Sol A. After 5 min, the required amount of AN was added dropwise, and the obtained mixture was stirred for 2 h in dark at 50°C.

At the end of the graft copolymerization, the mixture was continuously stirred for 15 min at room temperature, and then the pH raised to 10 by dropwise addition of 0.5 *M* NaOH solution to precipitate the product. Then the mixture was filtered to obtain the gelatinous precipitate. The solid mixture was washed by distilled water then by anhydrous alcohol to remove the salts and finally dried at 70°C to a constant weight. Thus, the crude product containing graft copolymer and homopolymer was obtained. To remove the PAN homopolymer, the crude product was poured in 100 mL of dimethyl formamide (DMF) and stirred gently at 50°C for 6 h.[17] After filtration, washed by DMF for several times, the pure chitosan-*g*-PAN was obtained by thoroughly washing with anhydrous alcohol and dried at 70°C to reach a constant weight.

The grafting percentage (GP) was calculated according to the following eq. (1)[24]:

$$\text{Grafting Percentage (GP)} = (A - B/B) \times 100 \quad (1)$$

where A and B are the weights of grafted product and chitosan, respectively. The grafted copolymers obtained with GP values 70, 160, and 250% were named $\mathbf{P}_1$, $\mathbf{P}_2$, and $\mathbf{P}_3$, respectively, as presented in Table I.

Hydrolysis of chitosan-*g*-PAN

The alkaline hydrolysis of chitosan-*g*-PAN grafted copolymer was carried out according to previous work of Ermakov et al.[26] Sodium hydroxide (20 mL 3%) solution was added to 0.5 g samples of chitosan-*g*-PAN with GP value of 250%. The mixture was stirred at 70°C for a desired period of time. After cooling to room temperature, 1 *N* solution of HCl was added with stirring until it became slightly acidic. The hydrolyzed grafted copolymer was then filtered and washed with distilled water then dried at 40°C. Hydrolyzed grafted copolymers (**HP**) after the reaction times 15, 30, and 45 min were, respectively, named as $\mathbf{HP}_1$, $\mathbf{HP}_2$, and $\mathbf{HP}_3$.

Characterization

Fourier transform infrared spectra (FTIR) were obtained with a Perkin-Elmer spectrophotometer with ATR accessory. The chitosan and modified chitosan were dried overnight at 60°C under reduced pressure and pressurized with a glass slide on top of the quartz window of the ATR instrument.

^{1}H-NMR spectra were recorded by an Oxford NMR instrument at 500 MHz at room temperature using D_2O/ CD_3COOD and NaSCN[22] as a solvent systems for native chitosan and chitosan-*g*-PAN, respectively.

TGA was performed on chitosan and modified chitosan by using a DuPont-2000 instrument. Experiments were performed with 2–3 mg of the sample under a dynamic nitrogen atmosphere flowing at a rate of 50 mL/min and at a heating rate of 10°C/min.

WAXD patterns of the samples were recorded on X-ray diffractometer (D/Max2500VB2+/Pc, Rigaku, Japan) with CuKα characteristic radiation (wavelength $\lambda = 0.154$ nm) at a voltage of 40 kV and a current of 50 mA. The scanning rate was 5°/min, and the scanning range of 2θ was from 5° to 55° at room temperature.

Swelling measurements

The water absorption was studied by soaking the dry grafted copolymer products in 20 mL of distilled water for 24 h at room temperature followed by weighing the wet polymer. The swelling ratio (SR%) was calculated according to the following eq. (2).

$$\text{Swelling ratio (SR\%)} = (W_1 - W_0/W_0) \times 100 \quad (2)$$

where W_0 is the weight of dry polymer and W_1 is the weight of swollen polymer.

Preparation of matrix tablets

The tablets were prepared by wet granulation technique in a similar way as described by Gavrilov et al.[27] Grafted copolymer powder (150 mg) under study and 18 mg of the MO drug model were mixed and granulated using ethanol as a granulating agent. The mass was dried and sieved through 20 mesh. The granules were lubricated and compressed into disk shape using IR hydraulic disk maker [Perkin-Elmer 1430] under a pressure of 400 kgf/cm^2 applied for 15 s of dwell time. Initially, a die of 10 mm diameter was filled with an exactly weighed quantity of the powder mixture using a little pressure, which gradually increased to 400 kgf/cm^2 of hydraulic pressure at a controlled rate.

In vitro release studies

To examine the effects of grafting reaction, hydrolysis of the grafted products, and release medium on drug release, the *in vitro* release studies were carried out in 300 mL of both simulated gastric fluid (SGF) (0.1 *M* HCl/KCl, pH = 1.2) and simulated intestinal fluid (SIF) (0.05 *M* phosphate buffer, pH = 7.1), as

the dissolution medium at 37°C. An aliquot of 2 mL was collected at regular intervals and the amount of MO released was measured colorimetry using visible light-UV spectrophotometer [Perkin-Elmer Lambda 3B] in a 1-cm cell at 520 nm for SGF and 450 for SIF.[28–30] Each *in vitro* release study was performed in triplicate.

RESULTS AND DISCUSSION

Synthesis of chitosan-*g*-PAN

The graft copolymerization of AN onto chitosan was performed by using $KMnO_4$ and oxalic acid as combined redox initiator system. Under such conditions, the first reaction is between MnO_4^- and the monomer, producing MnO_2 which in turn reacts with oxalic acid. This dissolution of manganese dioxide in sufficient excess of oxalic acid takes place rather quickly, producing carboxyl radicals, carbon dioxide, and the Mn(III)-oxalate complex. The cherry-red Mn(III) complex decomposes slowly in the course of a few seconds to a few minutes to form Mn^{2+} ions and carboxyl radicals as presented in the following equation.[23]

$$Mn^{3+} + C_2O_4^{2-} \longrightarrow Mn^{2+} + {}^{\bullet}C_2O_4^-$$

Free radicals of the type $^{\cdot}C_2O_4^-$ might attack the chitosan molecules giving chitosan macro-radicals, which initiate grafting of AN. Chitosan bears two types of reactive sites that can be grafted (Scheme 1), first, the free amino groups on deacetylated units and second, the hydroxyl groups on the C_3 and C_6 carbons on acetylated or deacetylated units.[1,2] Formulation details used in the synthetic procedures are summarized in Table I.

Characterization of the grafted copolymer

Figure 1 represent the FTIR-spectra of pure chitosan and chitosan-*g*-PAN with two different chitosan/PAN ratios The FTIR-spectrum of chitosan [Fig. 1(a)] exhibits various characteristic peaks, the most important one of them is the broad peak in the range of 3384 cm^{-1} to 3573 cm^{-1} due to HN—H and O—H stretching. However, in case of the IR spectra of $\mathbf{P}_1$ [GP = 70%, Fig. 1(b)] and $\mathbf{P}_3$ [GP = 250%, Fig. 1(c)], the appearance of sharp peaks at 2350 cm^{-1} (CN stretching), which is related to the cyano group of AN units, may confirm the presence of PAN grafted chains. The relative intensity of these peaks in each case may also reflect the extent of grafting, i.e., GP = 70% and 250% in case of $\mathbf{P}_1$ and $\mathbf{P}_3$, respectively.

The ^{1}H-NMR spectra of chitosan in D_3C COOD/D_2O and chitosan-*g*-PAN in NaSCN/D_2O solution were shown in Figure 2. The spectrum of chitosan

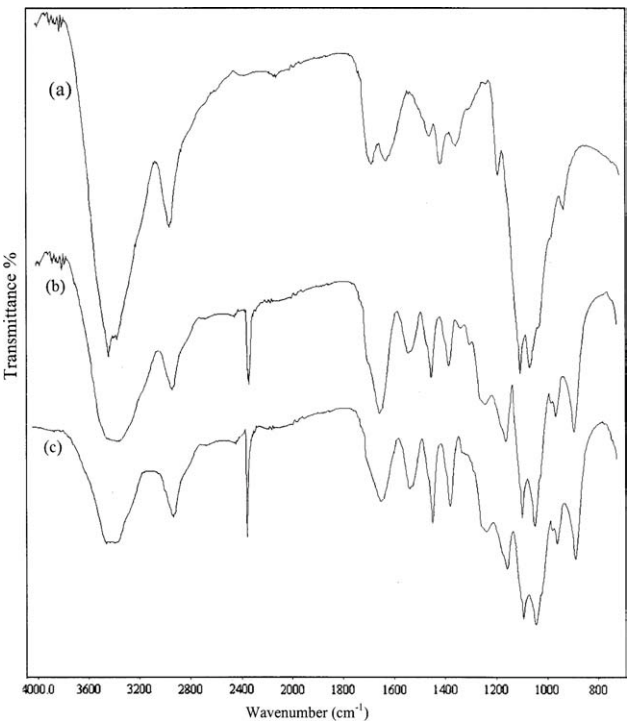


Figure 1 FTIR spectra of (a) chitosan, (b) chitosan-*g*-PAN ($\mathbf{P}_1$; GP 70%), and (c) chitosan-*g*-PAN ($\mathbf{P}_3$; GP 250%).

[Fig. 2(a)] shows a small peak at about δ 2.03 ppm assigned to the presence of $-CH_3$ of the *N*-acetylated glucosamine residue. The signal at δ 3.08 ppm was assigned to H^2 of glucosamine, and *N*-acetylated glucosamine and the multiplet peaks from δ 3.6 to 3.9 ppm were attributed to H^3, H^4, H^5, and H^6 of glucosamine and *N*-acetylated glucosamine. There existed a peak at δ about 4.78 ppm because of the presence of H^1 of glucosamine and *N*-acetylated glucosamine.[22]

As a representative example, the ^{1}H-NMR spectra is presented of $\mathbf{P}_1$ [Fig. 2(b)]. The spectrum confirms incorporation of the PAN grafted chains by the presence of typical peaks of PAN centered on 3.0 and 3.1 ppm corresponding to β-methylene and α-methine protons, respectively.[28] The signals at 3.7, 3.9, and 4.2 ppm might be due to interaction of chitosan with PAN in the NaSCN solution. These observations were in accordance with a previous report.[22] Anyway, Figure 2 also confirmed the grafting of PAN chains to chitosan to form copolymer.

The grafting was also supported by WAXD (Fig. 3). Chitosan itself exhibited typical peaks that appeared at $2\theta = 10°$ and 20°. These peaks were assigned to be a mixture of (001) and (100), and (101) and (002), respectively, while the more intensive peak of chitosan-*g*-PAN ($\mathbf{P}_2$) at around $2\theta = 17°$ was due to the overlapped diffraction peaks from the PAN's crystal planes of (110) and (200).[31] In the WAXD spectrum of chitosan-*g*-PAN, it is observed

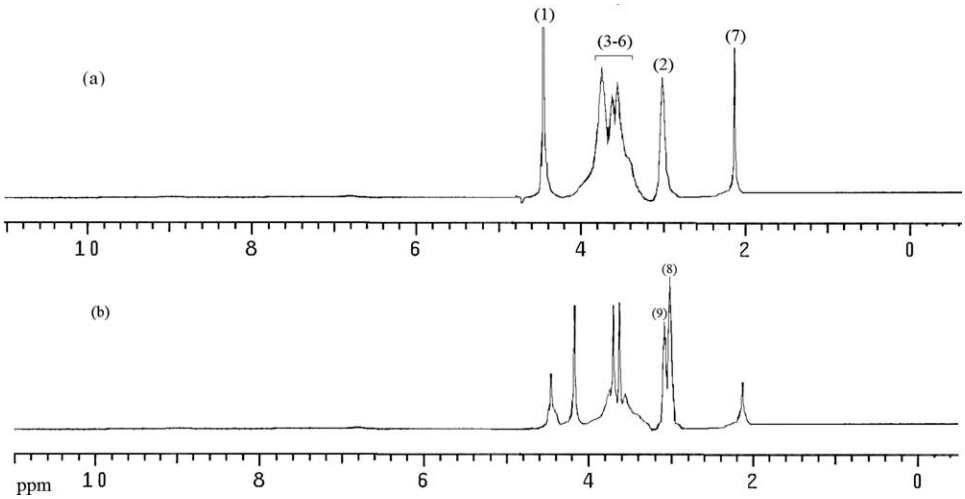


Figure 2 ^{1}H-NMR spectra of (a) chitosan in CD_3COOD/D_2O solvent system, (b) modified chitosan-g PAN ($\mathbf{P}_1$; GP 70%) in D_2O/NaSCN solvent system.

that diffraction intensity of the peak at around 20° was obviously weakened indicating that the crystallinity of the chitosan decreased after modification. PAN had grown into enough long chain to form the regular crystalline region during the graft copolymerization.

The TGA results of pure chitosan and chitosan-*g*-PAN ($\mathbf{P}_1$ and $\mathbf{P}_3$) were displayed in Figure 4. Pure chitosan, $\mathbf{P}_1$ and $\mathbf{P}_3$ exhibited an initial weight loss up to about 100°C, which may be due to presence of moisture. However, for pure chitosan, no weight loss occurred at the later stage, i.e., up to about 300°C, a rapid weight loss of about 50–55% is observed between 290°C and 370°C and this may be attributed to the splitting of the saccharide rings. These results were in accordance with previous report.[22] For the chitosan-*g*-PAN $\mathbf{P}_1$ and $\mathbf{P}_3$, the weight loss was observed at a later stages, i.e., about 350°C and 400°C for $\mathbf{P}_1$ and $\mathbf{P}_3$, respectively. Also, the modified chitosan-*g*-PAN polymer had a lower weight loss and higher residue of about 58% and 69% for $\mathbf{P}_1$ and $\mathbf{P}_3$, respectively, until 500°C. This supports that modification of chitosan by graft copolymerization of PAN renders chitosan thermally more stable. This may be due to the formation of a rigid polymer network, making it thermally more stable.

Hydrolysis of chitosan-*g*-PAN

Chitosan-*g*-PAN with GP value of 250% was hydrolyzed using aqueous sodium hydroxide solution at 70°C for 15, 30, and 45 min to give hydrolyzed chitosan-*g*-PAN with various extents in which a number of the functional cyano (—CN) groups were converted into carboxylic (—COOH) groups (Scheme 2).

The grafted copolymers obtained after 15, 30, and 45 min were, respectively, named as $\mathbf{HP}_1$, $\mathbf{HP}_2$, and $\mathbf{HP}_3$. FTIR spectra of chitosan-*g*-PAN with GP value of 250% and the corresponding hydrolyzed

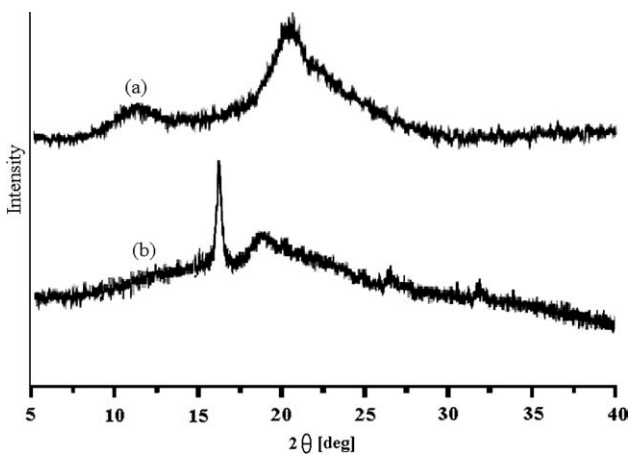


Figure 3 WAXD patterns of (a) chitosan, (b) chitosan-*g*-PAN ($\mathbf{P}_2$; GP 160%).

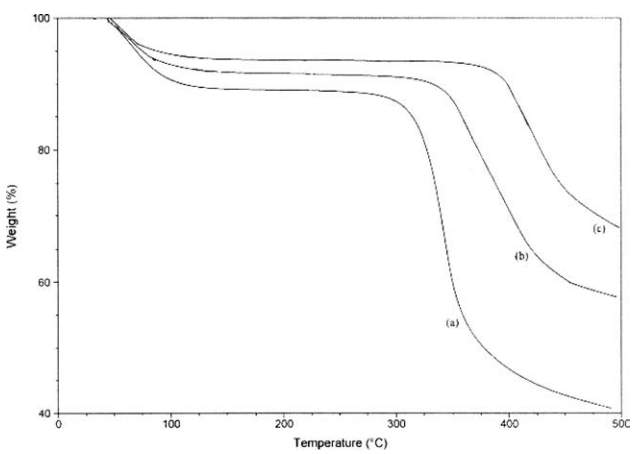
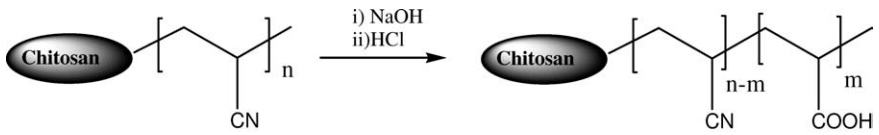


Figure 4 TGA thermogrames of (a) chitosan, (b) chitosan-*g*-PAN ($\mathbf{P}_1$), and (c) chitosan-*g*-PAN ($\mathbf{P}_3$).



Chitosan-g-PAN Hydrolyzed chitosan-g-PAN

Scheme 2 Partial hydrolysis of cyano groups in grafted PAN to carboxylic groups; $m/(n-m)$ ratio depend on the time of reaction.

copolymers are shown in Figure 5(a–d). Here the curves b, c, and d refer to hydrolyzed chitosan-*g*-PAN with GP 250%, **HP**$_1$, **HP**$_2$, and **HP**$_3$, respectively. FTIR spectra of the hydrolyzed copolymers show partial disappearance of the sharp intense peak of the —CN groups. Additionally, the strong peak at 3384 cm^{-1} related to —OH bonds becomes broad, and the intensity of the peak at about 1700 cm^{-1} corresponding to C=O group increases, which confirms the gradual conversion of the —CN groups into —COOH groups.

Swelling measurements

It was found that grafting with PAN caused a significant decrease of water absorption, when compared with pure chitosan (Table II). This trend may be due to the entering of the relatively more hydrophobic grafted polymeric chains, which may act as barrier against water absorption. Therefore, the higher hydrophobicity of grafted chitosan may explain their lower ability to bind water. However, the hydrolysis of the grafted copolymers causes a great increase in the water uptake, which increases as the extent of hydrolysis increase. This may be due to the partial conversion of the hydrophobic AN structural units into hydrophilic acrylic acid (AA) unites in the grafted chain.

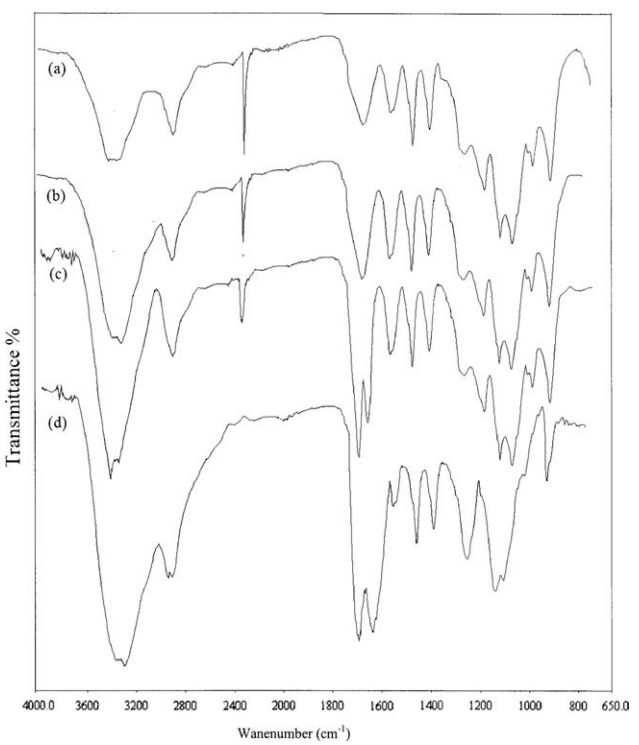


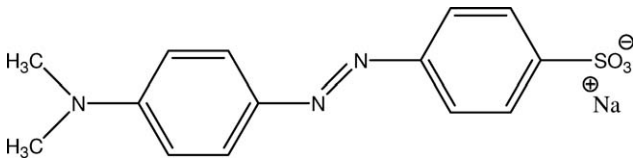
Figure 5 FTIR spectra of (a) Chitosan-*g*-PAN (GP 250%), (b) Hydrolyzed copolymer after 15 min (**HP**$_1$), (c) Hydrolyzed copolymer after 30 min (**HP**$_2$), and (d) Hydrolyzed copolymer after 45 min (**HP**$_3$).

APPLICATION OF CHITOSAN-*G*-ACRYLIC POLYMERS AS CARRIERS FOR THE FORMULATION OF DRUG DELIVERY SYSTEMS

The hydrolyzed and unhydrolyzed chitosan-*g*-PAN grafted copolymers were punched into matrix tablet after incorporation with MO, which was used as a drug model due to its availability, ease of estimation, its chemical structure (Scheme 3) which may be close to many types of drugs, in addition to the previous use for the same purpose in previous reports.[28–32] The release profiles of the drug model MO from the formulated tablets were performed in SGF and SIF media without enzymes. In this context, various tablets containing chitosan-*g*-PAN at various GP values and hydrolyzed grafted copolymers of different extents of hydrolysis were used [Fig. 6(a,b)]. Although the release profile of MO from the formulated tablets follows the same trend in both SGF and SIF media, the drug release was apparently influenced by the pH of release media, i.e., drug release in SGF was faster than that in SIF. It is perhaps reasonable to expect faster release in acidic medium than in neutral medium as the cationic chitosan based matrix shows a higher ability to swell in acidic medium due to the repulsion between the protonated unsubstituted amino groups (—NH_3^+), which may lead to higher erosion rate of the matrix

TABLE II
Swelling Measurements

Polymer	SR (%)
P$_1$	62
P$_2$	26
P$_3$	16
HP$_1$	140
HP$_2$	228
HP$_3$	304



Scheme 3 Chemical structure of methyl orange (MO) drug model.

tablets. It is evident that, in case of tablets containing chitosan-*g*-PAN with GP = 70%, 76% of the drug was released in SGF media within 24 h. However, tablets containing chitosan-*g*-PAN with higher GP values exhibited lower drug release under similar conditions. Thus, in cases of GP = 160% and 250%, only 66% and 51% of the drug were, respectively, released within 24 h. It is therefore, interesting to note that the increase of GP correlates with a decrease in the rate of drug release, suggesting that the PAN/chitosan-ratio in the copolymer carrier may significantly influence the rate of release. The observed slow release by increasing GP may be attributed to the increased hydrophobicity as a result of the increase of the PAN/chitosan-ratio, which may led to slower polymer chain relaxation under the employed condition.

In addition, tablets containing hydrolyzed chitosan-*g*-PAN with various extents of hydrolysis (**HP**$_1$, **HP**$_2$, and **HP**$_3$) released higher amounts of drug as compared to tablets containing unhydrolyzed chitosan-*g*-PAN under comparable conditions, i.e., **HP**$_1$, **HP**$_2$, and **HP**$_3$ released 62, 77, and 89% of the drug within only 12 h. This increase in the rate of release may be attributed to the conversion of more hydrophobic AN-units in the grafted PAN-chains into hydrophilic AA-units. As a result, the hydrophilicity of the copolymer will increase, so that the polymeric matrix may form loose channels within the network due to its hydrophilic nature and dissolution of hydrophilic polymers during the diffusion process. The formation of such loose channels leads to a decrease in the mean diffusion path length of the drug molecules to leach out into the diffusion medium, thereby resulting in higher rate of drug release from the polymeric matrix.

Mechanism and kinetics of drug release

The mechanism of drug release from matrices containing swellable or erodable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms.[33] The release data in SGF or SIF were fitted to the well-known Korsmeyer–Peppas eq. (3), which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well known or when more than one type of release phenomenon is involved.[33,34]

$$\log(M_t/M_f) = \log k + n \log t \tag{3}$$

where M_t/M_f is the drug released fraction at time (t), (k) is a kinetic constant incorporating the structural and geometric characteristics of the matrix tablets, (n) is the release exponent, indicative of the drug release mechanism. To determine n and k for different batches of matrices, the log value of drug-released fraction was plotted against the log time for each batch.

The mean dissolution time (MDT) was calculated from dissolution data using eq. (4),[35,36] and has been used for comparison.

$$\text{MDT} = (n/1+n).k^{-1/n} \tag{4}$$

In this study, the drug model (MO) release in acidic medium from matrix tablets containing

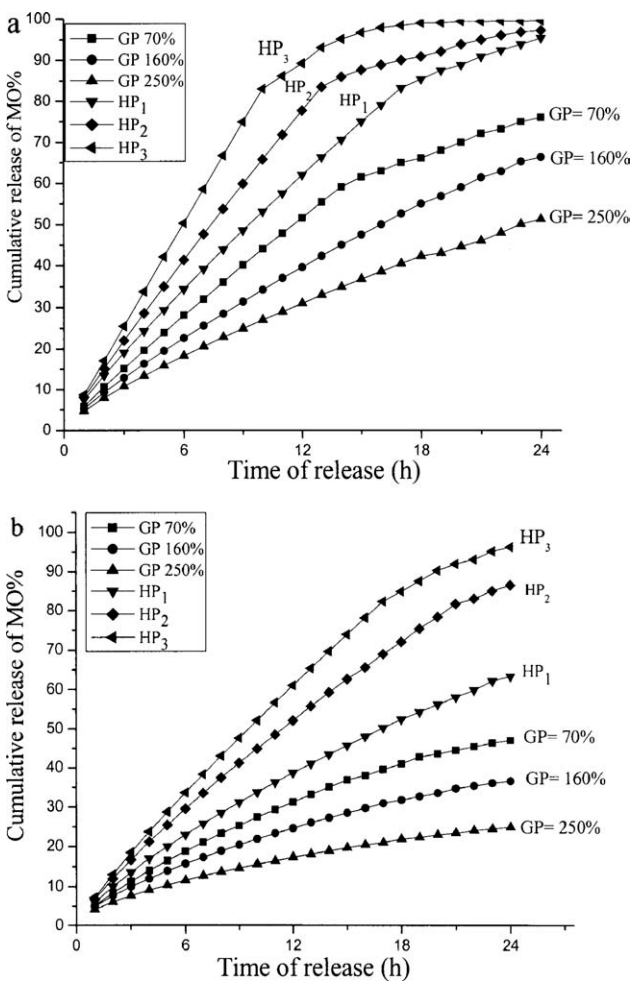


Figure 6 Release profiles of the drug model MO from the formulated polymer matrix tablets in (a) simulated gastric fluid (SGF) and (b) simulated intestinal fluid (SIF), plotted as a function of times.

TABLE III
Korsmeyer-Peppas Model Fitting of Release Data and Mean Dissolution Time (MDT) of Drug Model Formulations Based on Grafted Chitosan Matrix Tablets

Dissolution medium	Simulated gastric fluid (pH = 1.2) (SGF)						Simulated intestinal fluid (pH = 7.1) (SIF)					
Polymer (GP) (%)	$\mathbf{P}_1$ (70)	$\mathbf{P}_2$ (160)	$\mathbf{P}_3$ (250)	$\mathbf{HP}_1$	$\mathbf{HP}_2$	$\mathbf{HP}_3$	$\mathbf{P}_1$ (70)	$\mathbf{P}_2$ (160)	$\mathbf{P}_3$ (250)	$\mathbf{HP}_1$	$\mathbf{HP}_2$	$\mathbf{HP}_3$
Correlation coefficient (R^2)	0.997	1.01	0.989	0.97	0.995	0.996	0.996	0.989	1.00	0.978	0.999	0988
Kinetic conc (k) (h^{-1})	0.058	0.053	0.047	0.07	0.081	0.087	0.051	0.049	0.041	0.060	0.068	0.072
Diffusion exponent (n)	0.88	0.81	0.76	0.85	0.91	0.98	0.73	0.65	0.58	0.75	0.82	0.86
Order of release	N.F.	N.F.	N.F.	N.F.	S.C.II	S.C.II	N.F.	N.F.	N.F.	N.F.	N.F.	N.F.
$t_{1/2}$ (h)	11.6	16.0	22.5	9.3	7.4	6.0	22.8	35.7	74.6	17.0	11.4	9.5
MDT	11.90	16.81	24.12	9.67	7.54	5.98	24.87	40.78	90.47	18.24	11.95	9.85

N.F., non Fickian; S.C.II, super case II; $t_{1/2}$, release half time.

different types of hydrolyzed and unhydrolyzed chitosan-*g*-PAN showed a good fit into the Korsmeyer–Peppas equation, indicating a combined effect of diffusion and erosion mechanisms for drug release.[36] As illustrated in Table III, release data fit well with this model as a correlation coefficient (R^2) greater than 0.90 was obtained in all cases in acidic medium. The values of (n) and (k) were found to vary with the GP value and the extent of hydrolysis. Other authors[36] have reported similar n values. In this report, the release exponent (n) values ranged between 0.89 and 0.45 in case of drug release from chitosan-*g*-PAN in SGF, which suggests a non-Fickian or anomalous transport in which the drug release seemed to be controlled by both diffusion and erosion mechanisms. The values of n decreased, as the GP increased. This could be attributed to the decrease of the erosion rate by increasing GP, because the grafted hydrophobic PAN chains may act as barrier against the erosion of the chitosan backbone in the acidic medium.

In case of tablets containing hydrolyzed chitosan-*g*-PAN matrix $\mathbf{HP}_1$, $\mathbf{HP}_2$, and $\mathbf{HP}_3$, the n values are 0.85, 0.91, and 0.98, respectively, exhibiting a non-Fickian or anomalous transport in case of $\mathbf{HP}_1$ and a super Case II transport in case of both $\mathbf{HP}_2$ and $\mathbf{HP}_3$. This suggests that more than one mechanism may be involved, i.e., combination of polymer relaxation, erosion, and diffusion of the drug in the hydrated tablets matrices.

Drug release in SIF also fitted with the Korsmeyer-Peppas equation as a correlation coefficient (R^2) greater than 0.90 was obtained in all cases. The release exponent ranged between 0.58 and 0.73 for all chitosan-*g*-PAN matrices, exhibiting a non-Fickian transport. This means that the mechanism of release involves both diffusion and erosion mechanisms.

In case of tablets containing hydrolyzed chitosan-*g*-PAN matrix $\mathbf{HP}_1$, $\mathbf{HP}_2$, and $\mathbf{HP}_3$, the n values are 0.75, 0.82, and 0.86, respectively, exhibiting a non-Fickian anomalous transport in which the kinetics correspond to coupled diffusion and polymer relaxation mechanism. The higher values of n in SGF than SIF could be attributed to the higher erosion rate of the polymer matrix in acidic medium than in neutral medium.

CONCLUSIONS

Chitosan-*g*-PANs are of interest for use in the formulation of controlled drug delivery systems. Hydrophobic interactions are believed to enhance the stability of substituted chitosans via "hydrophobic self-assembly." It suggested that the release of drug is controlled by diffusion, erosion, or by swelling followed by diffusion and erosion, depending on both the GP value and the extent of hydrolysis of the grafted PAN chains.

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