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N-acylated chitosan: hydrophobic matrices for controlled drug release

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Abstract

N-acylation of chitosan with various fatty acid (C_6–C_{16}) chlorides increased its hydrophobic character and made important changes in its structural features. Unmodified chitosan exhibited a low degree of order (DO) and a weak tablet crushing strength. Chitosan acylated with a short chain length (C_6) possessed similar properties, but exhibited significant swelling. Acylation with longer side chains (C_8–C_{16}) resulted in a higher DO and crushing strength but lower swelling. The best mechanical characteristics and drug release properties were found for palmitoyl chitosan (substitution degree 40–50%) tablets with 20% acetaminophen as a tracer. The high stability of these monolithic tablets appears to be due to hydrophobic interactions between side chains, as shown by a more organized structure. Infrared spectroscopy, X-ray diffractometry and proton nuclear magnetic resonance analyses of palmitoyl chitosan were consistent with a hydrophobic self-assembling model. Drug dissolution kinetics showed longer release times for higher degrees of functionalization, i.e. 30 h (for 47% substitution) and 90 h (for 69% substitution), suggesting palmitoyl chitosan excipients as interesting candidates for oral and subdermal pharmaceutical applications.

Keywords: Chitosan; *N*-acylation; Hydrophobic self-assembling; Palmitoyl chitosan; Controlled release

1. Introduction

Interest in polymeric matrices for pharmaceutical formulation continues to grow. Special attention is currently given to chitosan, a polyaminoglucose obtained by partial deacetylation of chitin, the most abundant natural carbohydrate after cellulose [1]. X-ray diffraction data showed that chitin naturally exists in two mechanically resistant ordered crystalline structures stabilized by intra- and intermolecular hydrogen bonds [2–5]: α-chitin (antiparallel chains orientation) and β-chitin (parallel stacked units). Because of the high acetyl group content, chitin is insoluble in water and many organic solvents [6,7].

Deacetylation of chitin affords chitosan, mainly composed of 2-amino-2-deoxy-β-D-glucopyranose

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repeating units but still retaining a small amount of 2-acetamido-2-deoxy-β-D-glucopyranose residues. Chitosan with a high amino content ($pK_a \approx 6.2$–7.0) is water-soluble in aqueous acids [8]. The complete crystalline structure of chitosan has been described by Yui et al. [9]. Generally, three forms, hydrated, dehydrated and noncrystalline structures, of solid chitosan are found [10–12]. The crystalline structure of hydrated chitosan is a twofold helix, which can be converted to a dehydrated form, very similar to the hydrated form, but with the molecular packing and water content quite different [13]. The hydrated form (antiparallel) is stabilized by intramolecular O(3′)H···O(5) and intermolecular NH···O(6) hydrogen bonding and by hydrogen bridging involving water molecules. In the crystalline structure of the dehydrated form, parallel chains are organized in sheet structures via intermolecular C(2)NH···O(6) hydrogen bonds. Therefore, the transition from hydrated to dehydrated form requires cleavage of the C(2)NH···O(6) hydrogen bonds between antiparallel molecular chains and the formation of new C(2)NH···O(6) bonding between parallel polymer chains [9,12,13]. In addition, chitosan amino groups (at C2 position) are nucleophilic and reactive at higher pH values. They are a suitable site for chemical modifications and for enzyme immobilization [14,15]. Since chitosan itself is nontoxic [16], biodegradable [17,18] and biocompatible [19], several biological applications have been reported for chitosan, including chelation processes [20], a cholesterol trap [21,22] and a drug carrier [23]. Chitosan has been modified by cross-linking (e.g. with glutaraldehyde) to prepare «intelligent» drug delivery systems [24,25], and by carboxymethylation for repair and regeneration of bone tissues [26] or use as antioxidant agent [27]. Chitosan has also been conjugated with α-galactosyl for use as an inhibitor in acute rejection following xenotransplantation [28], with vinylsulfonate as an antimicrobial agent [29] and with sulfate as an activator of blood anticoagulant factors [30]. Recently, glycol chitosan was modified with palmitoyl *N*-hydroxysuccinimide to form vesicles [31,32] and hydrogels [33]. These derivatives present amphiphilic characteristics, stabilized by hydrophobic interactions, and exhibit erosion-controlled drug release for 5–7 h.

The present study describes the *N*-acylation of chitosan with fatty acyl chlorides to introduce hydrophobicity for use as matrix for drug delivery. It was expected that such derivatization would reduce hydration of the matrix and play a role in network stabilization by hydrophobic interactions. The structure of these derivatized chitosans was examined by Fourier-transform infrared (FT-IR), proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, and X-ray diffraction analysis, and the data compared to those of native chitosan.

2. Materials and methods

2.1. Materials

α-Chitosan (Kitomer™, MW 1600 kDa, 85–89% deacetylated) was obtained from Marinard Biotech (Canada). Palmitoyl chloride and caproyl chloride (Fluka Chemika, Switzerland), octanoyl chloride, myristoyl chloride, and other chemicals used in this study (Sigma-Aldrich Canada) were reagent grade and used without further purification.

2.2. Chitosan N-acylation

A mixture of chitosan (5 g) and aqueous acetic acid (600 ml, 0.12 M) was stirred for 24 h to ensure total solubility. The pH was adjusted to 7.2 by slow addition of 0.1 M NaOH with strong agitation, yielding a gel slurry, the volume of which was adjusted to about 900 ml. Palmitoyl chloride (20 ml, $d = 0.907$ g/ml) was then added and the reaction volume diluted to 1 l with distilled water. Similarly, different volumes (10–60 ml) of palmitoyl chloride were used to obtain various degrees of substitution. Other derivatives were obtained using the same conditions, substituting 20 ml of caproyl, octanoyl, or myristoyl chloride. After 4–6 h, each preparation was neutralized (pH 6.8–7.0) and precipitated with acetone. The precipitate, collected by filtration, was washed at 50–60 °C with an excess of methanol and decanted. The washing was repeated three times to eliminate free fatty acids (confirmed by the decrease and then stabilization of FT-IR peaks at 2850, 2950, 1555, and 1472 cm^{-1} in FT-IR spectra). Finally, the products were dried with pure

acetone to obtain the corresponding derivative powders.

2.3. Measurement of degree of acylation

2.3.1. By ninhydrin assay

The unchanged amino groups remaining after acylation were determined as described by Curotto and Aros [34]. Solutions of the acylated chitosan (0.1 mg/ml) were prepared in CH_3COOH (3% w/v) and HCl (1% w/v) by continuous stirring at 20 °C for 24 h. Acetate buffer (0.5 ml, 4 M, pH 5.5) was added to different volumes of the resulting chitosan solutions (0.1–0.5 ml, corresponding to 10–50 μg of chitosan). Ninhydrin Reagent (2 ml, Sigma, USA) was added and tubes were placed in a boiling water bath for 20 min. The solutions were cooled and their absorbances at 570 nm were read. D-glucosamine (Sigma) solutions (100% free amino groups) were used to generate a standard curve.

2.3.2. By FT-IR

The degree of *N*-acylation was also evaluated by FT-IR from the ratio of absorbance at 1655 cm^{-1} (ascribed to amide I band) and the hydroxyl band at 3450 cm^{-1}, applying the equation proposed by Moore and Roberts [35]:

$$DS(\%) = [(A_{1655}/A_{3450}) - 0.12] \times 100$$

Here DS is degree of substitution and the value 0.12 represents the acetyl groups specified in native chitosan. Powdered samples of acylated chitosan were compressed (2.3 T cm^{-2}) to obtain tablets (100 mg) for FT-IR analysis. For each sample, at least three tablets were used to obtain a statistical evaluation.

2.4. Mechanical properties

The crushing strength of tablets (500 mg each, obtained by direct compression at 2.3 T cm^{-2} of native or acylated chitosan powders, without tracer) was measured with an Erweka TBH 300 (Germany) device ($n = 5$ tablets for each derivative). The dimensions (thickness and diameter) of swollen tablets in phosphate buffer (0.05 M, pH 7.2) at 37 °C were evaluated with a digimatic indicator Id-110E (Mitutoyo, Japan) measuring initially (dry) and after 1, 4, 24, and 48 h swelling.

2.5. Structural analysis

2.5.1. Fourier-transform infrared (FT-IR) analysis

FT-IR spectra were recorded using a Spectrum One spectrophotometer (Perkin Elmer, USA) equipped with an Universal Attenuated Total Reflectance (UATR) device for tablet analysis in the spectral region (4000–650 cm^{-1}) with 64 scans recorded at a 4-cm^{-1} resolution.

2.5.2. X-ray diffraction

The diffraction patterns of native and acylated chitosan samples (powder and tablets) were recorded using a Siemens D-5000 diffractometer with a cobalt cathode operating in reflectance mode at wavelength of 1.79019 Å. The degree of order (DO) was expressed as $I/\Delta\theta$, where I is the intensity of diffraction maxima and $\Delta\theta$ is the width at half-peaks.

2.5.3. ^{1}H-NMR (proton nuclear magnetic resonance)

High-resolution ^{1}H-NMR spectra were recorded on a Bruker AMX2 500 spectrometer. Samples were prepared as described by Heux et al. [36]. Native or modified chitosan were dissolved at a concentration of 1% in deuterated water with HCl (pH 4.0). These solutions were then freezed/defreezed three times to exchange labile proton with deuterium and their spectra were recorded at 330 K.

2.6. Dissolution tests in vitro

Monolithic tablets (500 mg, 12.5-mm diameter, 3.0-mm thickness) of native or acylated chitosans containing 20% acetaminophen as a tracer were obtained by direct compression of powders (2.3 T cm^{-22} in a Carver hydraulic press). Tablets with increasing drug loading (i.e. 20%, 40%, and 60%) were prepared only for palmitoyl chitosan. The kinetics of drug release were recorded using a Distek™ dissolution 2100A paddle system (50 rpm) coupled with an UV Hewlett Packard spectrophotometer for detection of acetaminophen (280 nm) and presented using the diffusion equation [37] as the ratio of the amount of drug released at the time $t(M_t)$/the total amount (M_{inf}) of drug released from the tablet. The dissolution medium was 1-l phosphate buffer (0.05 M, pH 7.2) at 37 °C (USP XXV method).

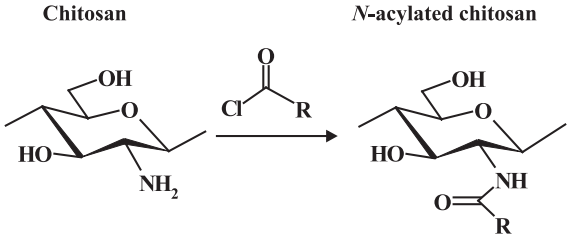
3. Results and discussion

3.1. Characteristics of acylated chitosan in powder and tablet forms

Two main aspects were examined in this study: the effect of acyl chains length (Scheme 1) and the degree of substitution (DS) on the structure and behavior of chitosan. It was found that only tablets based on acyl chitosan with a DS higher than 37% maintained their shape in solution for more than 4 h. For a DS lower than 37%, tablets disintegrated between 1 and 4 h. Table 1 presents the DS values determined by ninhydrin and FT-IR assays. No significant differences were noticed between the values obtained by these two assays.

3.1.1. FT-IR analysis

The absorption peaks at ca. 1655 cm^{-1} can be assigned to the carbonyl stretching of secondary amides (amide I band), at 1570 cm^{-1} to the N–H bending vibration of nonacylated 2-aminoglucose primary amines, and at 1555 cm^{-1} to the N–H bending vibrations of the amide II band [38]. The native chitosan (NC, nonmodified chitosan) used as starting material was reported by the manufacturer to have a degree of deacetylation of 85–89%. The presence of both 2-aminoglucose and 2-acetamidoglucose repeat units was confirmed by bands at 1655, 1570, and 1555 cm^{-1}. After *N*-acylation, the vibrational band corresponding to primary amino groups at 1570 cm^{-1} disappeared (Fig. 1), while prominent bands at 1655 and 1555 cm^{-1} were observed. In addition, peaks at 2850–2950 cm^{-1} were ascribed



R = $-(CH_2)_4CH_3$ → Caproyl chitosan (CC)
= $-(CH_2)_6CH_3$ → Octanoyl chitosan (OC)
= $-(CH_2)_{12}CH_3$ → Myristoyl chitosan (MC)
= $-(CH_2)_{14}CH_3$ → Palmitoyl chitosan (PC)

Scheme 1. Chitosan derivatization with fatty acyl chlorides.

Table 1
Estimation of degree of substitution by ninhydrin and FT-IR assays

Samples	Degree of substitution (%)	
	Ninhydrin assay	FT-IR
NC	15.4 ± 3.6	18.9 ± 2.1
CC	43.6 ± 3.2	46.2 ± 4.2
OC	41.8 ± 3.3	43.9 ± 3.8
MC	45.6 ± 3.8	47.1 ± 2.7
PC	44.4 ± 4.1	47.1 ± 3.6

NC = nonmodified chitosan; CC = caproyl chitosan; OC = octanoyl chitosan; MC = myristoyl chitosan; PC = palmitoyl chitosan.

to $-CH_2$; their intensity was proportional to the acyl chain length. These results clearly confirmed that the chitosan was substituted.

3.1.2. X-ray diffraction

Similar patterns were recorded for powders and the corresponding tablets. Therefore, only tablet diffractograms are presented. The crystalline structure of chitosan was gradually altered with the increasing acyl chain length (Fig. 2). The X-ray diffractogram of NC showed peaks of moderately low intensity and broader than those of octanoyl chitosan (OC) and myristoyl chitosan (MC). In the case of caproyl chitosan (CC) (short chain), the diffractogram showed only a diffuse peak (at 4.4 Å), broader than that of NC, suggesting that the crystallinity of NC was almost lost, probably due to a loss in hydrogen bonding. The low crystallinity of CC could be related to the pendant chain length, long enough to prevent hydrogen bonding and, at the same time, too short to induce hydrophobic stability. With longer acyl chains length (C_8–C_{14}), peaks became sharper; moreover, new peaks appeared at 19.4 Å for OC and 13.4 Å for MC. These major changes suggested a more crystalline and possibly more stable organization than for other forms of chitosan. PC clearly exhibited the highest degree of order. A similar profile was found for α-chitin (Fig. 2B), for which higher crystallinity due to *N*-acetate interchain C(2)NH... O=C(7) hydrogen bonding induces higher stability compared to less crystalline β-chitin [5]. Our results on chitosan modification suggest important changes in crystalline structure induced by the hydrophobic side chains. Furthermore, it seems that these hydrophobic interactions can enhance the stability and participate in a self-assembled network organization.

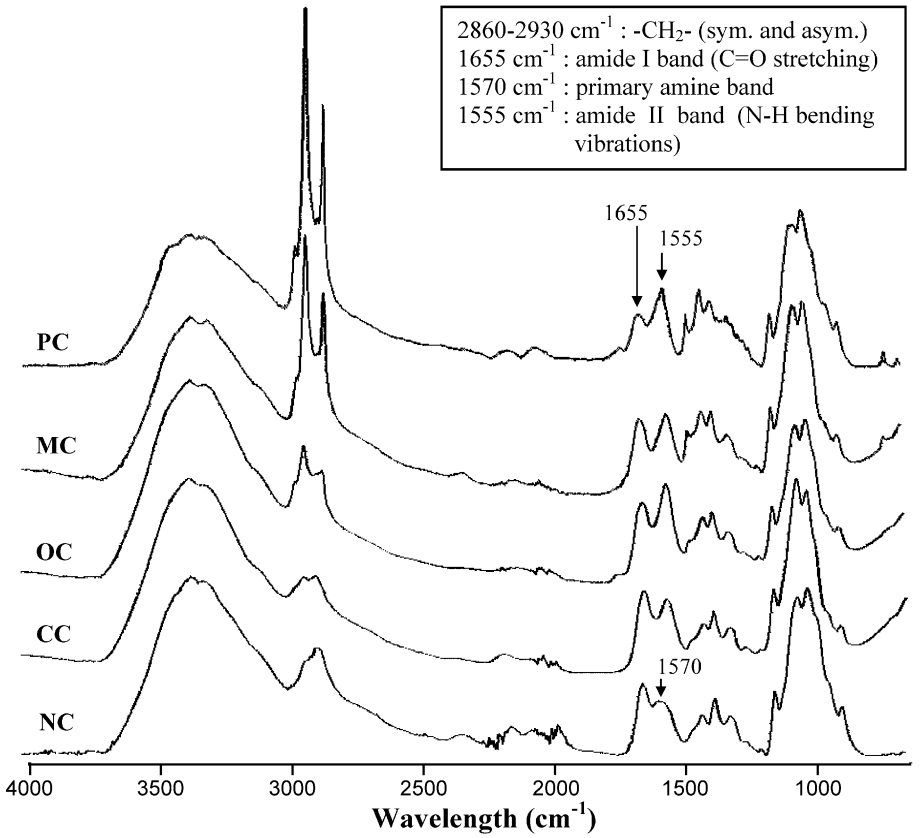


Fig. 1. FT-IR spectra of nonmodified and acylated chitosan with different acyl length (substitution degrees 40–50%): NC, nonmodified chitosan; CC, caproyl chitosan; OC, octanoyl chitosan; MC, myristoyl chitosan; PC, palmitoyl chitosan.

3.1.3. Mechanical properties

Good mechanical behavior was observed for CC and PC based-tablets on exposure to phosphate buffer, pH 7.2. These compositions maintained their integrity for 24 h. The CC tablets changed to a hydrogel with a swelling of 2.55 ml/g (two- to threefold its initial volume). No change of volume was noted for PC tablets. Surprisingly, OC and MC tablets disintegrated in 4–8 h. It can be concluded that the dependency on the length of acyl chains was nonmonotonous for swelling and nonlinear for the tablet integrity.

Fig. 3 represents the calculated degree of order (DO) of acyl chitosans in relation to the crushing strength and swelling volume. The DO of the crystalline structure was found to proportionally increase with acyl chain length, with the exception of CC (C_6), for which the DO slightly decreased (for reasons explained above) when compared to NC. This behavior suggests a higher crystallinity for longer acyl chains. A similar profile was observed for crushing strength. No significant difference was noticed between NC (9.3 ± 1.0 kp) and CC (10.1 ± 2.3 kp) tablets. For acyl chains of C_8 and longer, the crushing strength significantly increased and stabilized for C_8–C_{16} at about 18.5–22.5 kp. The explanation for this behavior may reside in the intensity of hydrophobic interactions, which for longer side chains and higher degree of substitution can stabilize the structure. In fact, the NC tablets showed a moderate–weak crushing strength, probably due to the hydrogen bonding. On the other hand, the increased crushing strength of functionalized chitosans (OC, MC, and PC) was related to hydrophobic interactions, which appear to be critically dependent of the length of the acyl chain.

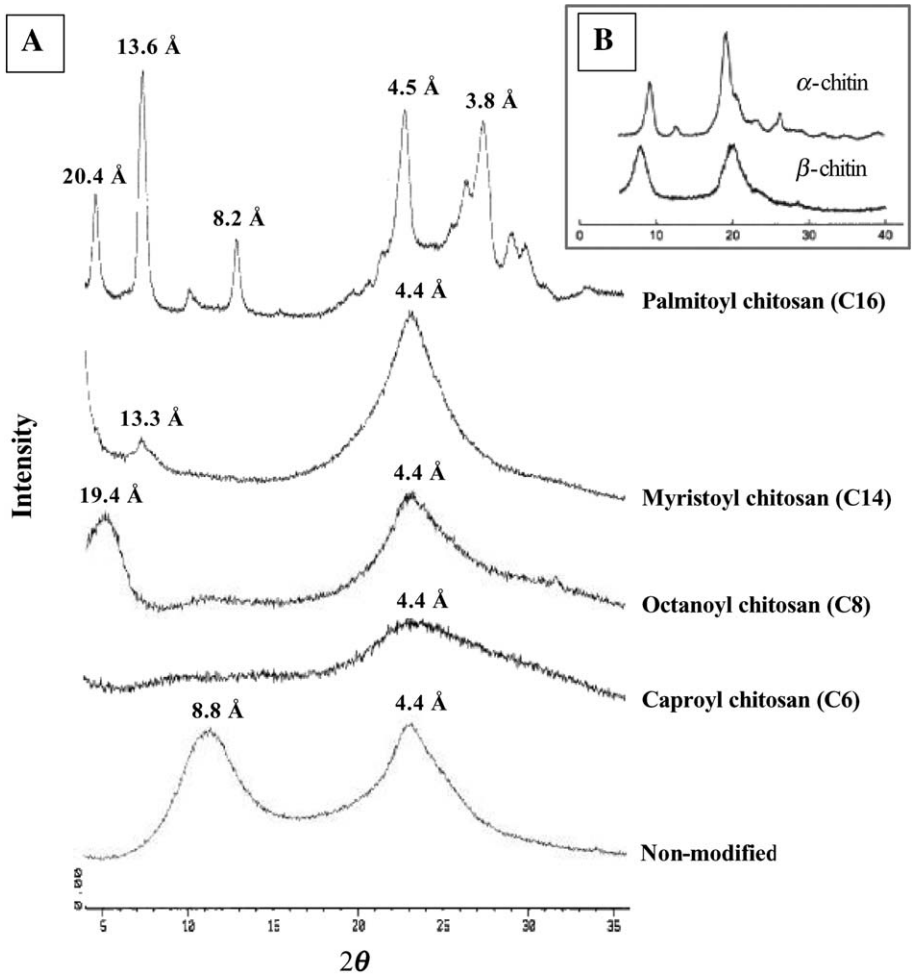


Fig. 2. X-ray diffractogram of (A) native and of acylated chitosan tablets and (B) of α- and β-chitin (adapted from Ref. [5]).

This can explain the weak crushing strength of CC with short acyl chains (C_6), generating low hydrophobic interactions. In contrast, for OC, MC, and PC, longer acyl chains induce more important hydrophobic interactions and, consequently, a higher crushing strength than that of CC (Fig. 3).

The chitosan derivative with short acyl chains (i.e. CC) exhibited significant swelling (two- to threefold of initial volume), creating a hydrogel texture. This could be explained by adjacent helix associations [7,39], still stabilized by hydrogen bonding but more amorphous than the other chitosans. The weak hydrophobic interactions in case of CC can still allow hydration and gelation. With the increase of acyl chains length, this capacity to hydrate was gradually lost, probably due to greater hydrophobicity, leading to very low swelling for OC, MC, and PC tablets (Fig. 3).

3.1.4. Drug release kinetics from acylated chitosan matrix

The release kinetics of acetaminophen from tablets obtained from chitosan derivatives with different length of acyl chains are presented in Fig. 4. The NC tablets rapidly disintegrated ($t_{90\%}$ ~ 1 h), whereas those based on acylated chitosans remained intact in aqueous medium (no erosion and no sticking being observed). The OC- and MC-based tablets showed relatively short release times ($t_{90\%}$

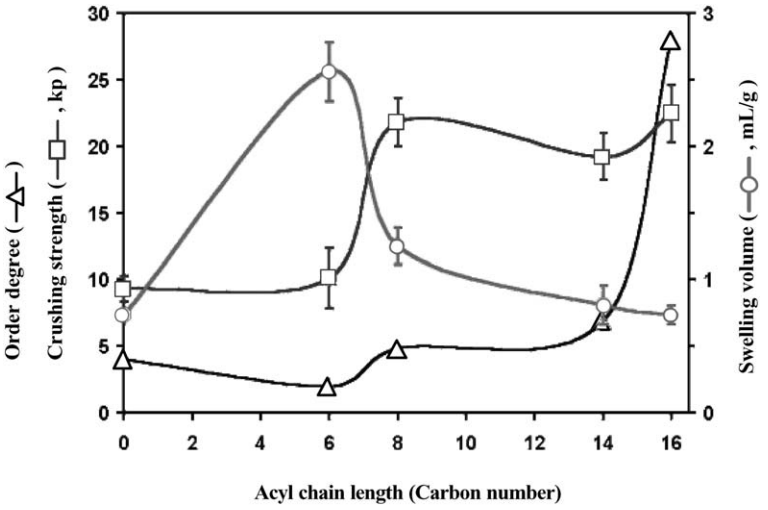


Fig. 3. Degree of order and mechanical properties of native and acylated chitosan with side acyl chains of various lengths (as presented in Scheme 1).

~ 4–6 h). A moderately long release (12 h) was observed for CC and a longer release (30 h) was recorded for PC. This could be attributed to a hydrophobic barrier limiting access of water and dissolution of the drug. Surprisingly, CC maintained better mechanical properties and preservation of tablet shape during the release than OC and MC. According to Peppas [37,40], there are three primary mechanisms by which the release of active agents can be controlled: erosion, diffusion, and swelling followed by diffusion. Erosion may take place via hydration or hydrolysis of the bulk, the polymer

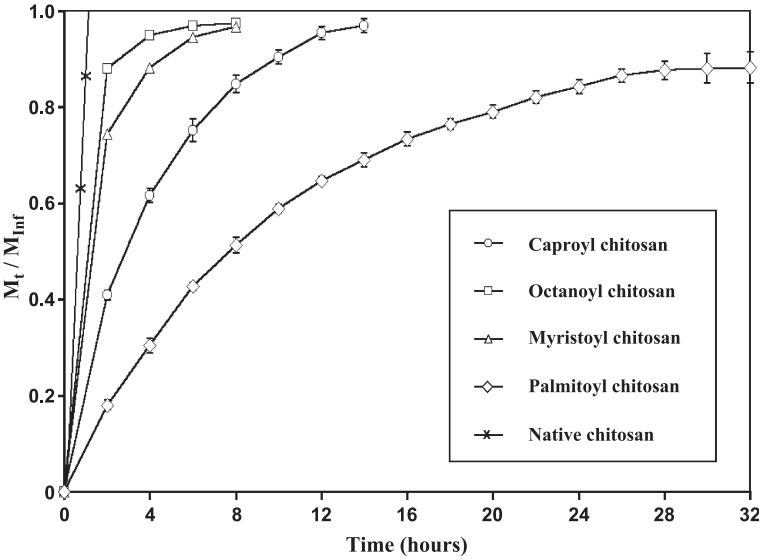


Fig. 4. Acetaminophen release profiles as a function of the length of the acyl chain of functionalized chitosan-based tablets (500 mg) containing 20% of active (tracer). The release kinetics were followed in 1 l of phosphate buffer (50 mM, pH 7.2), at 37 °C and 50 rpm, with a dissolution device Distek™ (Apparatus 2, USP XXV method).

being slowly degraded starting at the periphery of the tablet. Diffusion can occur through the unhydrated polymer matrix but will generally be facilitated as the polymer gradually swells in contact with the body fluids. The delivery mechanisms for CC and PC appeared totally different. In the case of the CC-based tablet (gel), the release mechanism may be controlled by swelling followed by diffusion, whereas for PC (no swelling) it may be based on diffusion alone.

Since the palmitoyl derivative exhibited the best mechanical and release characteristics, studies were continued with *N*-palmitoylated chitosan using different degrees of substitution to better evaluate their usefulness as controlled release systems.

3.2. Palmitoyl chitosan as a matrix for drug-controlled release

When compared to NC, the FT-IR spectra of PC with different degrees of functionalization (~ 28%, 47%, and 69%) showed a new band at 1570 cm^{-1} (amide II band). In addition, the spectra showed absorption at 2920–2850 cm^{-1} (acyl chain) increasing as a function of the substitution degree (Fig. 5), and a weak vibrational band at 1720 cm^{-1} (*O*-acylation) most noticeable for PC with the highest degree of functionalization (47% and 69%). Furthermore, there was an increase of the a and b peaks intensities at 3300–3100 cm^{-1} (Fig. 5), indicating lower intermolecular associations involv-

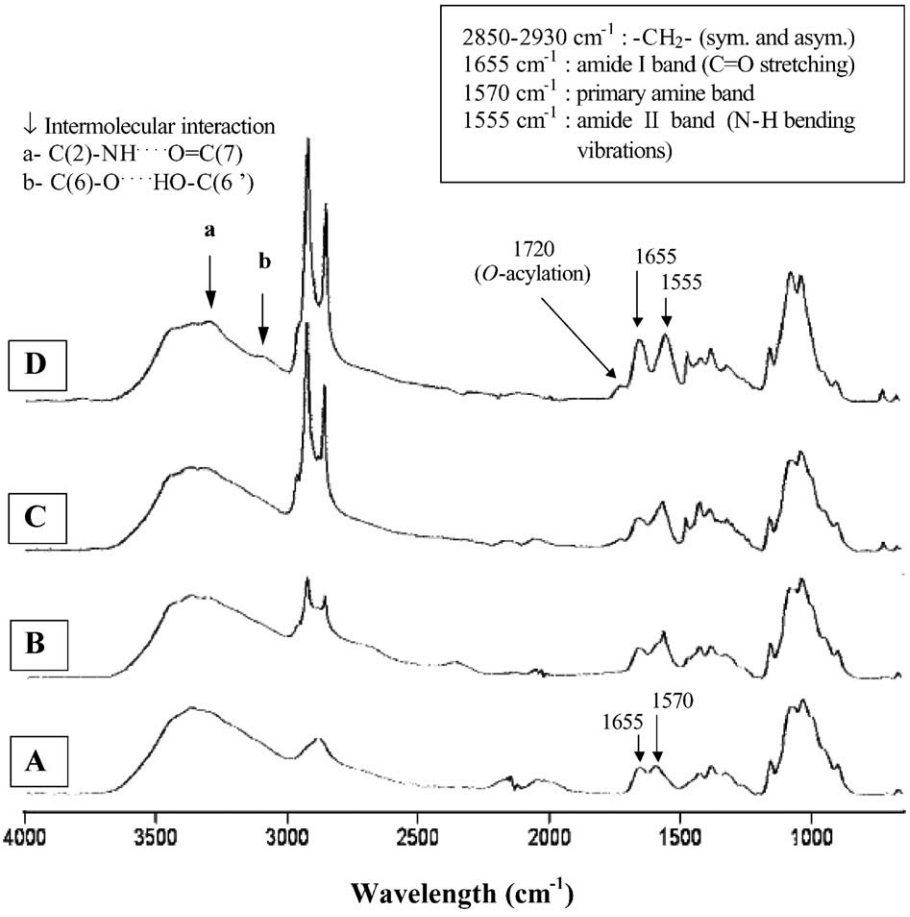


Fig. 5. FT-IR spectra of native chitosan (A) and palmitoyl chitosan with a degree of acylation of 28% (B), 35% (C), and 69% (D).

ing C(2)NH· · ·O=C(7) and C(6)OH· · ·O=C(7) hydrogen bonds [5]. This decrease in hydrogen bonding on acylation was particularly noticeable at high degrees of functionalization.

The ^{1}H-NMR spectra of NC and PC with 28%, 35%, and 47% DS are presented in Fig. 6 (for samples with 69% DS, the analysis was not possible, due to insolubility). For NC, peaks at 2.0–2.1 ppm can be ascribed to the three *N*-acetyl protons of *N*-acetylglucosamine (GlcNAc) and at 3.1–3.2 ppm to a H-2 proton of GlcNAc or glucosamine (GlcN) residues [38,41,42]. The ring protons (H-3, 4, 5, 6, 6′) are considered to resonate at 3.6–4.0 ppm. The peaks at 4.6 and 4.8 ppm were assigned to the H-1 protons of the GlcN and GlcNAc residues, respectively. New peaks at 0.7, 1.2, and 1.9 ppm ascribed respectively to CH_3, -CH_2- and -CH_2-(CO) of the palmitoyl residue appeared with intensities varying directly with the degree of palmitoylation. Observations from X-ray diffraction (Fig. 2) indicated that the PC structure contained more crystalline areas. It is also believed that NC can be essentially characterized by hydrogen bonding (Fig. 7A), whereas the PC is stabilized by hydrophobic interactions (Fig. 7B).

The hypothetical structure of PC compared with that of NC is schematically presented in Fig. 7. A higher degree of substitution would generate increasing hydrophobic interactions and enhance the stability following a «hydrophobic self-assembling» model [31]. This model fits well with the degree of substitution data (the intensity of hydrophobic interactions) and with acyl chain length [43]. In the case of short acyl chains (C_6), the gel character of CC can be attributed to helical association by hydrogen bonding and weak hydrophobic interactions. It is worth to mention that a higher degree of *N*-caproylation does not change the behavior of CC derivatives (data not shown). In the case of longer acyl chains length (C_{16}),

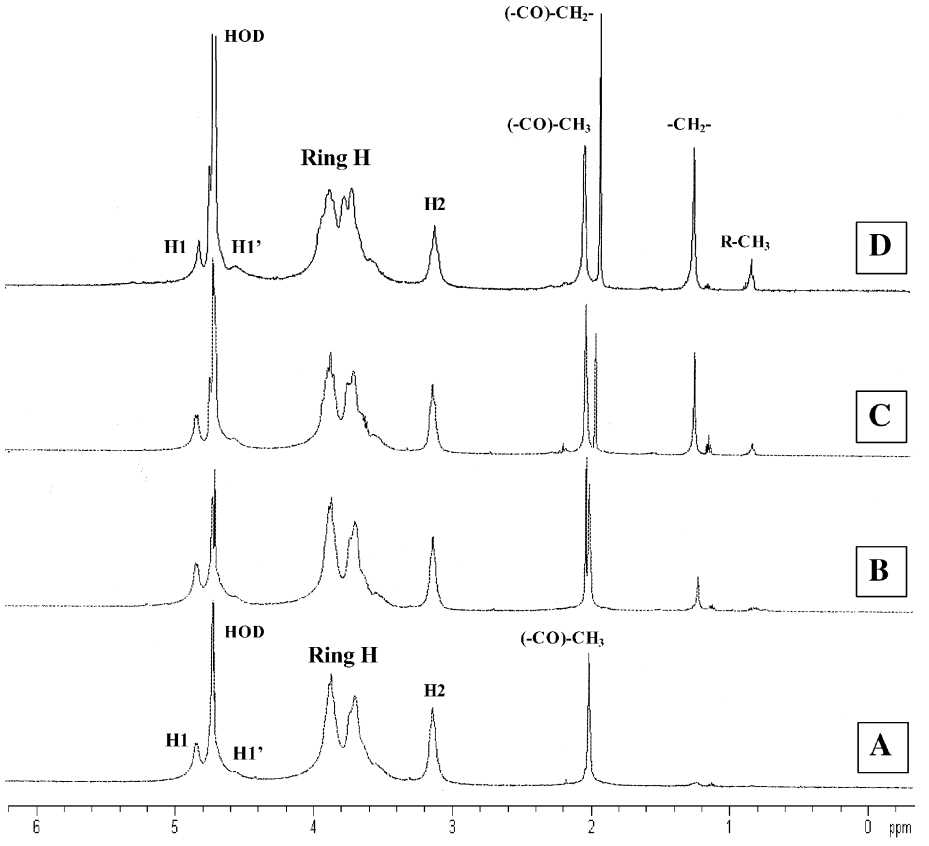


Fig. 6. ^{1}H-NMR spectra of native (A) and palmitoyl chitosan at 28% (B), 35% (C), and 47% (D) palmitoylation.

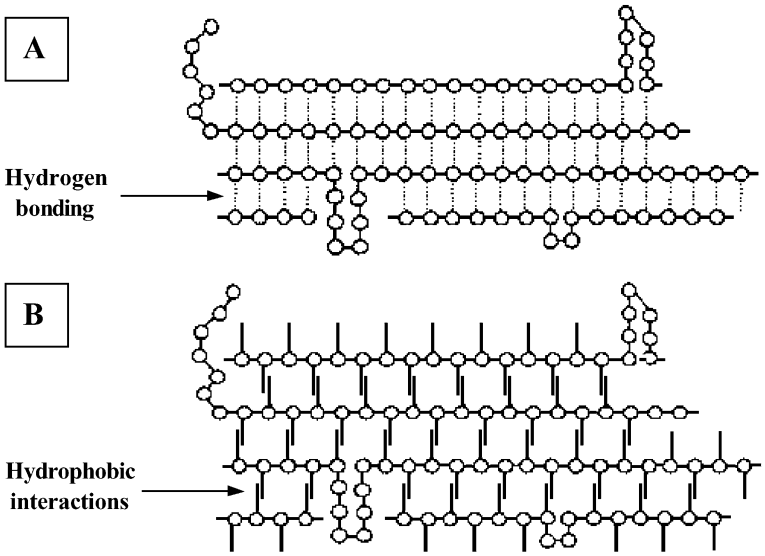


Fig. 7. Schematic presentation of network stabilization for native (A) and palmitoyl chitosan (B).

the polymeric matrix remained unchanged in aqueous media due to strong hydrophobic interactions. For medium-sized (C_8–C_{14}) chains, intermediate behavior was observed.

Control of drug release was improved by hydrophobic stabilization of matrices and the substitution degree, in agreement with previous reports by Noble et al. [32] and Martin et al. [33]. The palmitoyl chitosan described in this study is clearly different from the previously described amphiphilic palmitoyl glycol chitosan [31–33]. The later hydrogel formulations are obtained by freeze-drying aqueous dispersions of drug and palmitoyl glycol chitosan [33]. The novel palmitoyl chitosan here described can be obtained in powder form, allowing tablet formulation by direct compression of polymer and drug powders. The diffusion of drug is controlled by low water access. For tablets based on PC with 47% DS (Fig. 8A), the kinetics of drug release persisted for up to 30 h even with high drug loading (40% and 60% of acetaminophen). On the other hand, the kinetics of drug release by PC tablets with 69% DS were dependent on the initial drug loading (Fig. 8B). For tablets with 20% of drug, the duration of release was up to 90 h. For higher drug loads, the duration of release decreased, to 50 h for 40% and 30 h for 60% of drug. The explanation of this phenomenon may reside with drug solubility, particularly in the case of hydrophilic drugs that alter the hydrophilic/hydrophobic character of the system. At high drug loading (60%), there is an increase of hydration creating pores, which favor drug diffusion. In this case, the release profile is very similar to PC with 47% DS ($t_{90\%}$ = 30 h).

Consequently, formulations based on acylated chitosan with DS between 40% and 50% have release rates appropriate for oral administration; formulations with DS higher than 50% have release times longer than 24 h and are less useful for oral dosage forms but can be of great interest as implants. However, implants must be compatible with blood and tissues. Until now, no extensive study has been reported on the biocompatibility of PC. Lee et al. [44] reported several *N*-acylated chitosan (propionyl, butyryl, pentanoyl, and hexanoyl chitosan) derivatives possessing better hemocompatibility than *N*-acetyl chitosan. This compatibility, higher for longer acyl side length, was explained by a higher susceptibility of longer chain *N*-acyl chitosans to enzymatic degradation by lysozyme. It was also considered that the degree of substitution of *N*-acylated chitosans contributed to their biodegradability. Furthermore, Tokura and Tamura [26] showed that certain bioactivities of chitosan in animals differ as a function of the availability of amino groups and that acylation was an important factor in achieving biocompatibil-

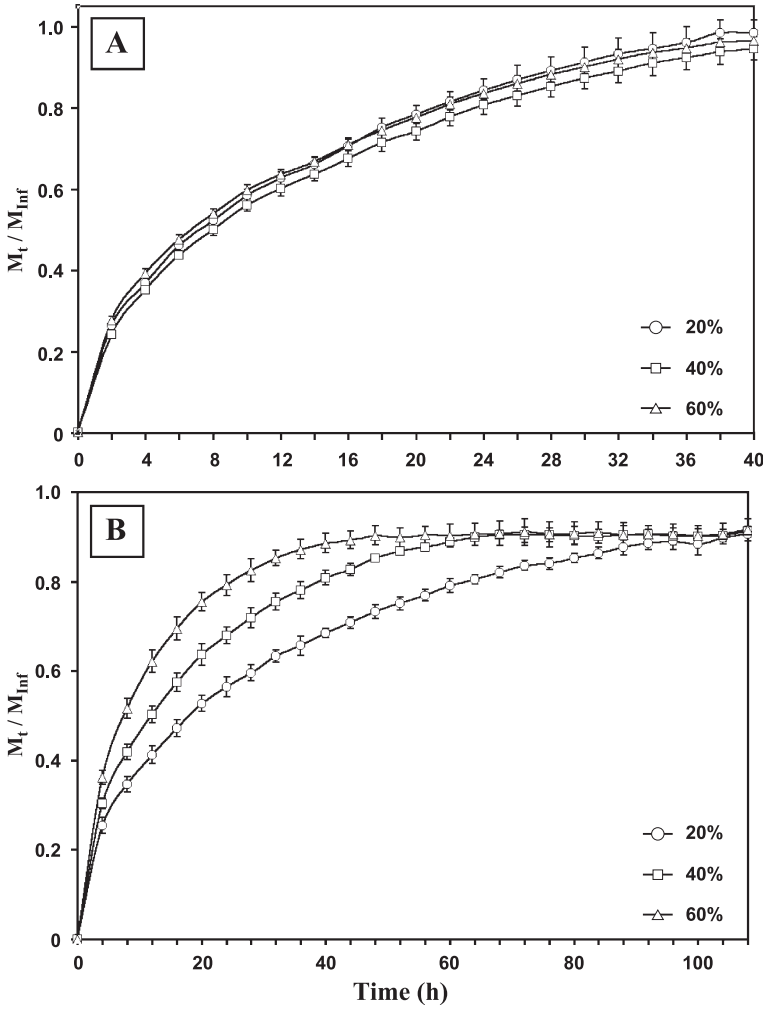


Fig. 8. Release profiles of acetaminophen from tablets (500 mg) based on palmitoyl chitosan with 47% (A) and 69% degree of substitution (B), containing 20%, 40%, and 60% of drug (dissolution conditions as described at Fig. 4).

ity. Consequently, chitosan having a high degree of high palmitoylation seems of interest as an implant for controlled release of bioactive compounds such as antibiotics, steroids, peptide hormones, contraceptives, etc. useful for human and veterinarian therapy.

4. Conclusion

N-acylated chitosans are of interest for use as excipients in 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, or by swelling followed by diffusion, depending on both the acyl chain length and the degree of acylation.

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