Drug physical state and drug–polymer interaction on drug release from chitosan matrix films

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Abstract

Four different grades of chitosan varying in molecular weight and degree of deacetylation were used to prepare chitosan films. Salicylic acid and theophylline were incorporated into cast chitosan films as model acidic and basic drugs, respectively. Crystalline characteristics, thermal behavior, drug–polymer interaction and drug release behaviors of the films were studied. The results of Fourier transform infrared and solid-state 13C NMR spectroscopy demonstrated the drug–polymer interaction between salicylic acid and chitosan, resulting in salicylate formation, whereas no drug–polymer interaction was observed in theophylline-loaded chitosan films. Most chitosan films loaded with either salicylic acid or theophylline exhibited a fast release pattern, whereas the high viscosity chitosan films incorporated with salicylic acid showed sustained release patterns in distilled water. The sustained release action of salicylic acid from the high viscosity chitosan films was due to the drug–polymer interaction. The mechanism of release was Fickian diffusion control with subsequent zero order release. It was suggested that the swelling property, dissolution characteristics of the polymer films, pKa of drugs and especially drug–polymer interaction were important factors governing drug release patterns from chitosan films. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Chitosan films; Salicylic acid; Theophylline; Drug release; Drug–polymer interaction

1. Introduction

Chitosan, a cationic natural biopolymer produced from deacetylation of chitin, has been widely used for drug carrying devices in controlled drug delivery systems [1]. A drug–polymer dispersion can be utilized to accomplish coating of non-pariel seeds, yielding a matrix for diffusion-mediated controlled drug release. In addition, a drug–polymer matrix film may be adaptable for transdermal drug delivery [2]. The incorporation of a drug into a chitosan matrix to form a monolithic device can expand the use of this biopolymer. Up to date, the study of drug-loaded chitosan films were focused on release behavior of the drug from chitosan matrix films [3–6]. Depending on the amount of chitosan [4], film thickness [4,5], and dissolution medium [4], the liberation of drug from the chitosan films varied from fast release...
to slow release. In case of the sustained release, it was reported that the drug was released from the chitosan film following zero order [5] or first order kinetics [6]. Imai et al. [7] found the interaction of indomethacin with low molecular weight chitosan (MW 3800–25,000) and reported the improved release of the drug.

Many grades of chitosan are available with different molecular weights and degree of deacetylation (%DD) [1,8]. In the previous paper, we studied the physicochemical characteristics of chitosan films prepared from four types of chitosan derived from crab shell chitin, that is, very low-viscosity grade (VL type, MW 50,000–60,000) with 82%DD; very low-viscosity grade (VL type, MW 50,000–60,000) with 100%DD; high-viscosity grade (H type, MW 800,000–1,000,000) with 80–85%DD; and high-viscosity grade (H type, MW 600,000–800,000) with 100%DD [9]. The characteristics of chitosan films prepared depended on its molecular weight and degree of deacetylation. Therefore, it is of interest to investigate the effect of molecular weight as well as degree of deacetylation of chitosan on the release behavior of drug from chitosan matrix films. In addition, drug physical state and molecular interaction of drugs with chitosan of different grades in the films were also investigated using salicylic acid and theophylline as acidic and basic model drugs, respectively. Crystalline characteristics and thermal behavior of drugs in the chitosan films were studied by powder X-ray diffraction and differential scanning calorimetry. Fourier transform infrared (FTIR) spectroscopy and solid-state 13C nuclear magnetic resonance (NMR) spectroscopy were used for characterization of the molecular interaction between drug and chitosan in the films. Finally, the relation of the molecular interaction of drug with chitosan to the drug release behavior from chitosan matrix film was discussed.

2. Materials and methods

2.1. Materials

Four types of chitosan derived from crab shell chitin varying in molecular weight and degree of deacetylation (%DD) i.e. very low viscosity grade (VL type, MW 50,000–60,000) with 82%DD, very low viscosity grade (VL type, MW 50,000–60,000) with 100%DD and high viscosity grade (H type, MW 800,000–1,000,000) with 80–85%DD and high viscosity grade (H type, MW 600,000–800,000) with 100%DD were given as gifts from Dainichiseika Colors and Chemicals Manufacturing, Japan. The H-type chitosan is a high viscosity grade (1000–2000 cps, 0.5% w/w in 1% w/w acetic acid solution at 20°C) where the VL-type chitosan is a very low viscosity grade (5±1 cps, 1% w/w in 0.5% w/w acetic acid solution at 20°C) (data obtained from the manufacturer). Salicylic acid was purchased from Nacalai Tesque, Japan. Theophylline USP (anhydrous) was purchased from Armend: Drug and Chemical, USA. All other chemicals were of reagent grade.

2.2. Preparation of drug-loaded chitosan films

Salicylic acid or theophylline was either dissolved or dispersed in 1% w/w chitosan acidic solution at 10–90% w/w drug loadings using 1% v/v acetic acid as a dissolving vehicle. The drug containing solution was then cast in a dish with a diameter of 43.5 mm and dried at 60°C for 7–9 h.

2.3. Morphology study

The morphology of chitosan films loaded with salicylic acid or theophylline at various concentrations was observed under a scanning electron microscope (model JSM 4510, Jeol, Japan). The samples were attached to the slab surfaces with double-sided adhesive tapes and then coated with gold to thickness about 30 nm under vacuum to make the samples conductive. Scanning electron photomicrographs were taken at appropriate magnification.

2.4. Powder X-ray diffraction study

Powder X-ray diffraction patterns of chitosan films loaded with various concentrations of salicylic acid or theophylline, pure drugs, and drug–polymer physical mixtures were measured using powder X-ray diffractometer (model JDX-3530, Jeol, Japan) with Ni-filtered Cu radiation generated at 30 kV and 30 mA as an X-ray source.
2.5. Differential scanning calorimetry (DSC)

The DSC thermograms of pure drug and chitosan films loaded with salicylic acid at a concentration range of 10–90% w/w were recorded. The sample of 2–4 mg was accurately weighed into a liquid aluminum pan with cover sealed. The measurements were performed under nitrogen purge over 50–200°C at a heating rate of 20°C/min.

2.6. Fourier transform infrared (FTIR) spectroscopy

Transmission infrared spectra of chitosan films loaded with various concentrations of salicylic acid or theophylline, pure drugs, and drug–polymer physical mixtures were measured by using a Fourier transform infrared spectrophotometer (model Magna-IR™ system 750, Nicolet, USA). The FTIR spectrum of a chitosan film prepared from VL-100%DD chitosan using salicylic acid as a dissolving vehicle was also measured. The powders were measured by KBr method and the films were directly measured for FTIR spectra.

2.7. Nuclear magnetic resonance (NMR) spectroscopy

$^{13}$C NMR spectra of chitosan films loaded with 10% salicylic acid or theophylline using acetic acid as a dissolving vehicle, pure drugs and a VL-100%DD chitosan film using salicylic acid as a dissolving vehicle were obtained by using the high resolution solid-state $^{13}$C NMR spectrometer (model DPX-300, Bruker Switzerland). The spectra were recorded by means of the cross polarization-magic angle spinning (CP-MAS) method at 75.46 MHz using a Bruker z-32DR $^{13}$C-MAS probe. The contact time for cross polarization was 1 ms. The 90° pulse width was 5 ms and repetition time was 4 s. $^{13}$C chemical shifts were calibrated indirectly through the use of adamantane (29.5 ppm from tetramethysilane).

2.8. In vitro drug release study

The release of salicylic acid or theophylline from 10% drug-loaded chitosan films was evaluated using the USP dissolution apparatus V (paddle over disk, Pharmatest™, Germany) in distilled water. The paddles were rotated at 50 rpm at temperature 32±0.5°C for transdermal drug delivery. Salicylic acid and theophylline (anhydrous) were analyzed by using a UV spectrophotometer (Perkin Elmer, Lambda 2). The analytical wavelength of salicylic acid and theophylline in distilled water were 296 nm and 272 nm, respectively. All the experiments were done in triplicates.

3. Results and discussion

3.1. Morphology study

The scanning electron photomicrographs of VL-82%DD chitosan films loaded with 30% and 40% salicylic acid are illustrated in Fig. 1. The drug crystals were observed at 40% drug loading (Fig. 1b) and they were clearly observed by visual inspection at higher than 40% drug loading. In the films prepared from VL-100%DD, H-80–85%DD, and H-100%DD chitosan, the drug crystals appeared at 50% drug loading and they were also observed by visual inspection at higher than 50% drug loading. The drug crystals were clearly observed in all types of chitosan films loaded with 10% theophylline and higher, indicating crystallization of theophylline during film formation. Two crystal forms of theophylline, needle-like and plate-like crystals were observed in all films. Rodriguez-Hornedo et al. [10,11] and Otsuka et al. [12] reported that the plate-like crystal was anhydrous crystal of theophylline, which would change to the needle-like crystal of monohydrate form in the presence of water or high humidity. It indicated that theophylline crystallized in anhydrous or monohydrate crystal forms when processing into chitosan films.

3.2. Powder X-ray diffraction

Powder X-ray diffraction patterns of 10–40% salicylic acid loaded in VL-82%DD chitosan films are shown in Fig. 2. The diffraction peaks associated with drug crystal molecules in VL-82%DD chitosan films were observed at 40% drug loading while those in the films prepared from VL-100%DD, H-80–
85%DD, and H-100%DD chitosan were observed at 50% drug loading. The results indicated that salicylic acid molecule existed in an amorphous form or monomolecularly dispersed state in the VL-82%DD chitosan films at less than 40% drug loading and in VL-100%DD, H-80–85%DD, and H-100%DD chitosan films at less than 50% drug loading. The results were consistent with the data observed from SEM photomicrographs of chitosan films loaded with salicylic acid.

The powder X-ray diffraction peaks of anhydrous theophylline in this study was assigned to the form II according to the Suzuki et al. study [13]. When loading 10–40% anhydrous theophylline into chitosan films, the drug crystalline peaks were observed at 10% drug loading and higher (Fig. 3). The diffraction peaks associated with both anhydrous and monohydrate theophylline were observed as well as in VL-100%DD, H-80–85%DD, and H-100%DD chitosan films loaded with anhydrous theophylline. It seemed that theophylline in chitosan films existed in both anhydrous and monohydrate crystalline forms. There have been many studies reported the phase transition of hydrate and anhydrous theophylline [10–14]. Rodriguez-Hornedo et al. [10,11], Otsuka et

showed a sharp melting peak of salicylic acid powder at onset temperature of 157°C (Fig. 4). The drug melting peaks were observed at 40% drug loading and higher. In the other films prepared from VL-100%DD, H-80–85%DD and H-100%DD chitosan, the drug melting peaks were observed at 50% drug loading and higher. The intensity and the sharpness of the endothermic peak increased with the increasing drug concentrations. The limiting percent of drug dissolved in films at its melting temperature, in other words, solid-state solubility, was determined from the y-intercept of the plot between the heat of melting ($\Delta H_m$, J/g of drug) and the drug concentration in film [17,18]. As a result, the solid-state solubility of salicylic acid in VL-82%DD chitosan film was estimated as 32% (Fig. 5). It indicated that salicylic acid molecules in the VL-82%DD chitosan films containing drug less than 40% existed in a dissolved state and at concentration higher than its al. [12,14] and Herman et al. [15] reported that the transformation of anhydrous theophylline to monohydrate form took place when being recrystallized from an aqueous buffer supersaturated solution or processed during wet granulation or even stored at high humidity condition. The phase transformation of theophylline monohydrate to anhydrous theophylline was about 60–70°C [16]. It was suggested that the crystallization below the phase transformation point would provide the monohydrate crystal. In this study, the chitosan films were dried at 60°C, which was closed to the transformation point. This may result in the crystallization of both anhydrous theophylline and theophylline monohydrate in the films.

3.3. Differential scanning calorimetry

DSC thermograms of VL-82%DD chitosan films loaded with salicylic acid at various concentrations

Fig. 3. Powder X-ray diffraction patterns of VL-82%DD chitosan films loaded with theophylline (TH) at various % drug loading, (a) 40%TH film, (b) 30%TH film, (c) 20%TH film, (d) 10%TH film, and (e) VL-82%DD chitosan powder. (A, anhydrous theophylline; M, theophylline monohydrate).

Fig. 4. DSC thermograms of salicylic acid powder (SA), and VL-82%DD chitosan films loaded with salicylic acid at various % drug loading.
3.3. Drug–polymer interaction

3.3.1. Fourier transform infrared spectroscopy (FTIR)

The transmission infrared spectra of VL-82%DD chitosan film loaded with 10% salicylic acid is shown in comparison with chitosan free film, and salicylic acid powder in Fig. 6. The IR spectrum of chitosan showed the asymmetric and symmetric solid-state solubility the drug existed in crystalline form as well as in a dissolved state. The solid-state solubility of salicylic acid in films prepared from VL-100%DD, H-80–85%DD, and H-100%DD chitosan were estimated as 41%, 36%, and 44%, respectively. It was noted that the degree of deacetylation of chitosan affected the solid-state solubility of salicylic acid in chitosan films. As the degree of deacetylation increased the solid-state solubility increased. It might be attributed to the higher amino group content in chitosan with high degree of deacetylation that might interact with salicylic acid, resulting in increasing the solid-state solubility. Moreover, the influence of molecular weight of chitosan on the solid-state solubility was also observed. At the same range of degree of deacetylation, the solid-state solubility of drug in films slightly increased as the molecular weight of chitosan increased. This might be attributable to the difficulty of crystallization of drug in high molecular weight (high viscosity) chitosan during film formation [19–21]. Consequently, the more dissolved state of drug was anticipated in the films obtained from high molecular weight chitosan solution, resulting in higher solid-state solubility value.

Fig. 6. Transmission infrared spectra of VL-82%DD chitosan films loaded with salicylic acid, (a) VL-82%DD chitosan film, (b) VL-82%DD chitosan film loaded with 10% salicylic acid, and (c) salicylic acid.
carboxylate anion stretching at 1565 cm$^{-1}$ and 1411 cm$^{-1}$, respectively, indicating that chitosan molecules in the free film was in the form of chitosonium acetate [9]. In the IR spectrum of salicylic acid, the carboxyl carbonyl stretching peak was observed at 1656 cm$^{-1}$ [22]. When loading salicylic acid into chitosan film, changes in the IR spectrum were observed. The carbonyl stretching peak at 1655 cm$^{-1}$ (amide I peak), representing the N-acetyl functional group of chitosan disappeared and a new peak at 1628 cm$^{-1}$ assigned to an asymmetric NH$_2^+$ bending was observed [23]. The new peak was also observed at 1384 cm$^{-1}$, which was assigned to the symmetric carboxylate anion stretching of salicylate anion. Similar IR spectra were observed in the salicylic acid-loaded chitosan films prepared from chitosan of the other grades. In order to clarify this change in IR peaks, the IR spectrum of VL-100%DD chitosan film using salicylic acid as a dissolving vehicle instead of acetic acid was measured. The spectrum was found to be similar to the spectra of all salicylic acid-loaded chitosan films using acetic acid as a dissolving vehicle. It was therefore confirmed that salicylic acid might interact with chitosan at the position of an amino group to form salicylate salt. Furthermore, the IR spectra of the physical mixtures between salicylic acid and chitosan indicated no change in peaks of the drug and the polymer, suggesting no drug–polymer interaction in the physical mixtures. In addition, no change in the IR peaks of the drug and polymer was observed in all chitosan films loaded with theophylline as well as those in the drug–polymer physical mixtures.

3.4.2. Nuclear magnetic resonance (NMR) spectroscopy

The $^{13}$C NMR spectra of chitosan films loaded with 10% salicylic acid are illustrated in Fig. 7. The resonances around 24, and 180 ppm were assigned to CH$_3$ carbon and carbonyl carbon. These peaks demonstrated that chitosan molecules existed in the form of chitosonium acetate as it had been reported in the Toffey et al. [24] and our previous studies [9]. The resonances around 175 ppm might be assigned to a carbonyl carbon of salicylate group. It demonstrated the presence of salicylic acid in the form of salicylate salt, when loaded into the chitosan films. The supportive data was shown by the $^{13}$C NMR spectra of salicylic acid, sodium salicylate, and VL-100%DD chitosan film prepared by using salicylic acid as a dissolving vehicle instead of acetic acid (Fig. 8). The resonance at 173 ppm, assigned to COOH carbon of salicylic acid (Fig. 8c), would shift to more downfield at 176 ppm in the solid-state...
Fig. 8. Solid-state $^1$C NMR spectra of (a) VL-100%DD chitosan film prepared by using salicylic acid as a dissolving vehicle, (b) sodium salicylate, and (c) salicylic acid (data simulated by computer).

NMR spectrum, assigned to COO$^-$ carbon of salicylate moiety in the chitosan films, and in sodium salt form (Fig. 8a and b) [21]. Though the resonances at 174 ppm in chitosan films with lower degree of deacetylation were associated with N-acetyl CO carbon of chitosan [24], this resonance could be assigned to COO$^-$ carbon of salicylate salt form. Therefore, it may be concluded that salicylate salt
formation might occur when loading the drug into chitosan films. In addition, no drug–polymer interaction was observed from the data of \(^{13}\text{C}\) NMR spectra of all chitosan films loaded with theophylline.

### 3.5. In vitro drug release study

The dissolution profiles of salicylic acid from 10% drug-loaded chitosan films into distilled water are illustrated in Fig. 9. The drug released rapidly from the VL-type chitosan films and reached 100% within 1–1.5 h. In the case of the H-type chitosan films, the sustained release behavior was observed. The amount of drug released from H-80 to 85% DD and H-100% DD chitosan films during 24 h reached 95% and 74%, respectively. In addition, the release of theophylline from all chitosan films was fast release. We reported that VL-type chitosan films swelled and dissolved rapidly in distilled water [9]. The H-type chitosan films swelled extensively and slowly dissolved with gradual erosion into small fragments, which could last in distilled water more than 24 h. The rapid drug release from VL-type chitosan films was attributed to the rapid dissolution of the polymer in distilled water even when there was the drug interaction between salicylic acid and chitosan. The sustained release action of salicylic acid from the H-type chitosan films was mainly due to the drug–polymer interaction since the slow dissolving of the H-type chitosan did not affect the drug release of theophylline. The release mechanism of salicylic acid from the H-type chitosan films up to 50–60% was Fickian following the exponential equation as illustrated by \(M_t/M_{\infty}\) versus \(t^{1/2}\) plot and Higuchi’s model (Fig. 10) [25,26]. The subsequent drug release higher than 60% was zero order release. The drug release from the H-100% DD chitosan film was sustained release action of salicylic acid from the slower than that from H-80 to 85% DD chitosan film. The H-80–85% DD chitosan film gave a much higher swelling index than the H-100% DD film [9], indicating a more loose structure of the swollen film. The slower drug release from the H-100% DD films might be attributed to the denser and more viscous network of the swollen films as well as the higher amino content and thus more extensive drug–polymer interaction. It was suggested that the swelling property, the dissolution characteristics of the polymer films, the \(pK_a\) of the drug and the drug–polymer interaction were important factors governing the drug release patterns from chitosan films.

### 4. Conclusion

Physicochemical characterization of all chitosan films loaded with salicylic acid and theophylline could reveal the drug physical state and drug–polymer interaction. The solid-state solubility of salicylic
acid in chitosan films was about 32–44% at its melting temperature. The higher the molecular weight and degree of deacetylation of chitosan the higher the solid-state solubility was. The drug existed in an amorphous state or monomolecularly dispersed in the films like solid-state solution when loaded at concentration less than its solid-state solubility. Theophylline existed in both monohydrate and anhydrous forms in all chitosan films. The data of FTIR and solid-state $^{13}$C NMR spectroscopy demonstrated the drug–polymer interaction between salicylic acid and chitosan at an amino group, resulting in salicylate formation, whereas no drug–polymer interaction was observed in the theophylline-loaded chitosan films. The drug–polymer interaction affected the release of salicylic acid from the high viscosity chitosan films resulted in sustained release action. It was summarized that chitosan could interact with negatively charged (acidic) drugs when incorporated into films and this might affect the drug release characteristics as well as the physicochemical property of the drug and polymer.

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