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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 ^{13}C 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, pK_a of drugs and especially drug–polymer interaction were important factors governing drug release patterns from chitosan films.

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

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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 ^{13}C 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 tetramethylsilane).

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.

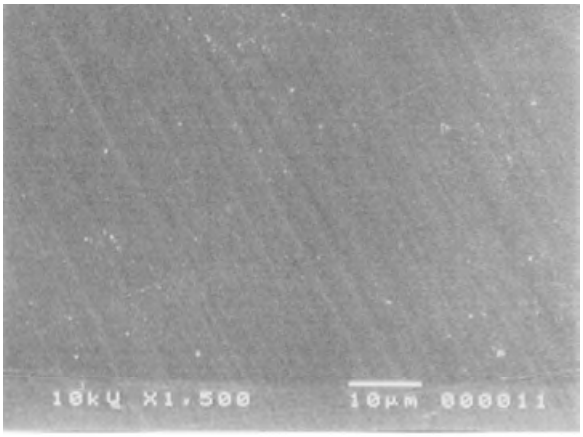
3. Results and discussion

3.1. Morphology study

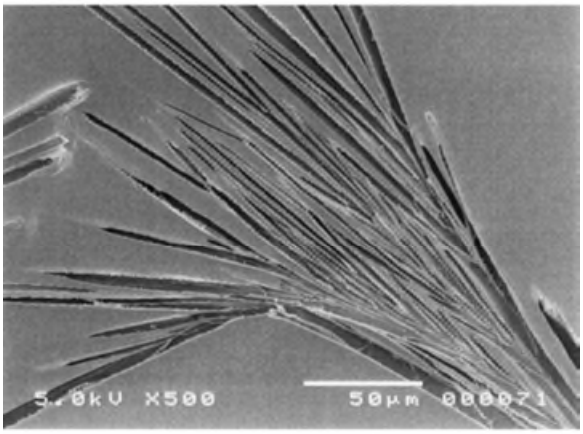
The scanning electron photomicrographs of VL-82%DD chitosan films loaded with 30% and 40% salicylic acid are illustrated in Fig. 1. The drug crystals were observed at 40% drug loading (Fig. 1b) and they were clearly observed by visual inspection at higher than 40% drug loading. In the films prepared 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–



(a)



(b)

Fig. 1. Scanning electron photomicrographs of VL-82%DD chitosan films loaded with salicylic acid at different % drug loading, (a) 30%, and (b) 40%.

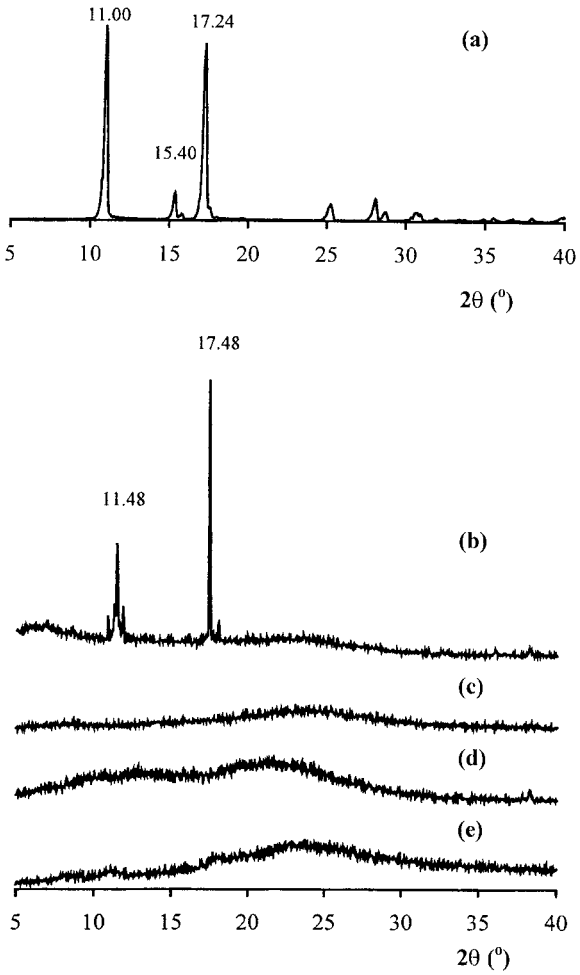


Fig. 2. Powder X-ray diffraction patterns of VL-82%DD chitosan films loaded with salicylic acid (SA) at various % drug loading, (a) SA powder, (b) 40% SA film, (c) 30% SA film, (d) 10% SA film, and (e) VL-82%DD chitosan film.

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

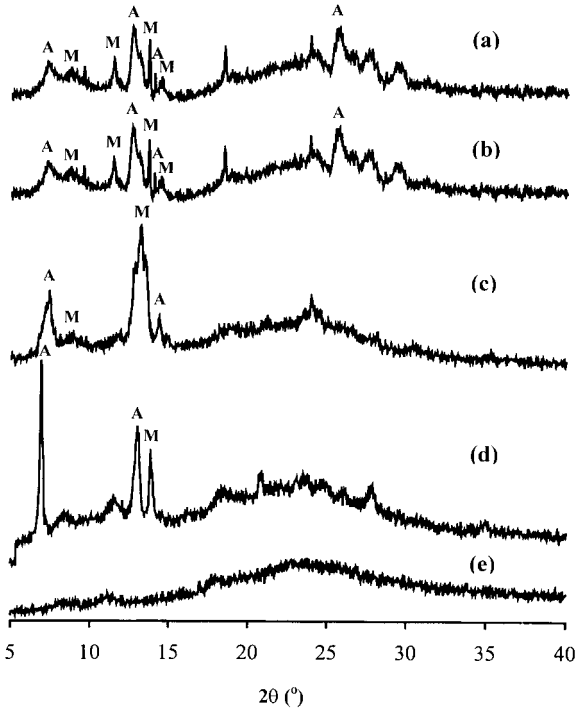


Fig. 3. Powder X-ray diffraction patterns of VL-82%DD chitosan films loaded with theophylline (TH) at various % drug loading, (a) 40%TH film, (b) 30%TH film, (c) 20%TH film, (d) 10%TH film, and (e) VL-82%DD chitosan powder. (A, anhydrous theophylline; M, theophylline monohydrate).

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 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 (ΔHm, 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

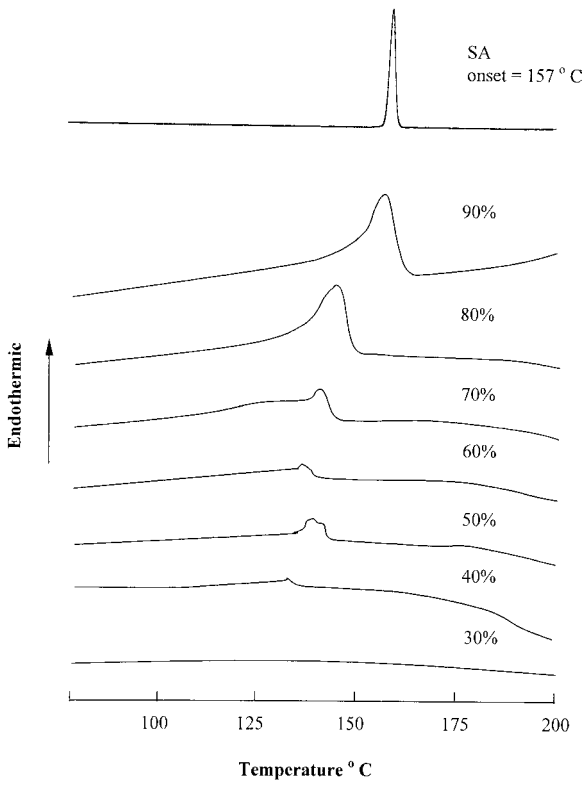


Fig. 4. DSC thermograms of salicylic acid powder (SA), and VL-82%DD chitosan films loaded with salicylic acid at various % drug loading.

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