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RESEARCH PAPER

Effect of Heat on Characteristics of Chitosan Film Coated on Theophylline Tablets

Jurairat Nunthanid,[1,*] Suchada Wanchana,[1] Pornsak Sriamornsak,[1] Sontaya Limmatavapirat,[1] Manee Luangtana-anan,[1] and Satit Puttipipatkhachorn[2]

[1]*Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand*
[2]*Faculty of Pharmacy, Mahidol University, Sri-ayudhya Road, Bangkok 10400, Thailand*

ABSTRACT

The effect of heat on the characteristics of chitosan film coated on theophylline tablets was studied. Chitosan of high viscosity grade with molecular weight in the range of 800,000–1,000,000, 80–85% degree of deacetylation was used as a film former by dissolving in 1% v/v acetic acid solution. The coated tablets had been cured at 40, 60, and 100°C for 6, 12, and 24 hr. The morphology of the film at the edge and surface of coated tablets was investigated using scanning electron microscopy. Film cracking was increased and clearly observed in the coated tablets cured at 100°C for 24 hr. As a result, more water could be absorbed into the tablets, followed by faster disintegration and faster drug release. The evidence of partial conversion of chitosonium acetate to chitin in the ^{13}C nuclear magnetic resonance (NMR) spectra of chitosan films cured at 40, 60, and 100°C was observed, but it had no effect on drug release behavior. Theophylline tablets coated with chitosan films gave sustained release behavior in various media, i.e., distilled water, 0.1 N hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. In addition, the film coating temperature at 55–60°C and curing process at 40 and 60°C had no effect on the drug release from theophylline tablets

*Corresponding author. Fax: (6634) 255801; E-mail: jrr@su.ac.th or jurairat@email.pharm.su.ac.th

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coated with chitosan polymer. Finally, it might be concluded that both the physical and chemical properties of chitosan films were affected by heat.

Key Words: *Chitosan; Theophylline; Film characteristics*

INTRODUCTION

Chitosan is a natural biopolymer produced by alkaline *N*-deacetylation of chitin, the most abundant natural polymer found widely in shrimp shell, crab shell, and cell wall of bacteria and fungi. It becomes an interesting material in pharmaceutical applications, especially as a film former, due to its biodegradability, biocompatibility, and low toxicity.[1–3] Chitosan is insoluble in water, sulfuric acid, and phosphoric acid, but readily soluble in hydrochloric acid as well as various organic acids such as acetic acid, lactic acid, propionic acid, and citric acid.[1,4–6] It also forms a gel at low pH and can easily be formed into a film by the casting technique.[7–11] Chitin is insoluble in water and soluble in organic solvents such as dimethylacetamide (DMAC/LiCl) and hexafluoroisopropanol.[2,12,13] Its solubility property makes it difficult to prepare chitin film.

Nunthanid et al.,[14] using Fourier transform infrared spectroscopy and solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopy, reported that chitosan films prepared by casting of dissolved chitosan in an aqueous acetic acid were chitosonium acetate films, which were water-soluble. The high molecular weight chitosan films were much slower to dissolve in distilled water than the low molecular weight ones. Toffey et al.[15] found that the conversion of a water-soluble chitosonium acetate film into a water-insoluble chitin film was induced by heat. The evidence of change was investigated by using solid-state ^{13}C NMR spectroscopy. Lim and Wan[16] also reported the heat effect on decreasing the solubility of chitosan films. Kanke et al.[8] studied the release of prednisolone from chitosan and chitin films. They found that the drug release from chitin films was slower than that from chitosan films. Few studies have so far been performed on the application of chitosan in tablet film coating. It was known in general that the temperature of film coating processes in pharmaceutical coating technology was about 50–70°C. The curing process of the film-coated products, as well as the coating temperature, might change the properties of the films, especially chitosan films, resulting in an effect on drug release behavior.

The aim of the present study was to investigate the influence of heat on the characteristics of chitosan film coated on theophylline tablets. The core tablets were prepared by direct compression process using Avicel pH-102 as diluent. Chitosan of high viscosity grade, with degree of deacetylation about 80–85%, was dissolved in acetic acid as a film-coating solution. The film was coated on theophylline tablets using an air atomizer with drying temperature about 55–60°C. The coated tablets had been cured at 40, 60, and 100°C for 6, 12, and 24 hr. The morphology of the cured tablets was observed using scanning electron microscopy. Tablet disintegration was investigated in distilled water, and drug release from the cured tablets was investigated in distilled water, 0.1 N hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The molecular structure of chitosan films cured at 40, 60, and 100°C for 24 hr was examined using Fourier transform infrared spectroscopy and solid-state ^{13}C NMR spectroscopy.

MATERIALS AND METHODS

Materials

Chitosan, derived from chitin crab shell, of high viscosity grade (H-type, molecular weight 800,000–1,000,000) with 80–85% degree of deacetylation was given as a gift from Dainichiseika Colors and Chemicals Mfg. Co. Ltd., Tokyo, Japan. The H-type chitosan is a high viscosity grade (1000–2000 cps, 0.5% w/w in 0.5% w/w acetic acid solution at 20°C) (data obtained from the manufacturer). Chitin was purchased from Kyowa, Technos Co., Chiba, Japan. Theophylline USP (anhydrous) was purchased from Armend: Drug and Chemical Inc., Irvington, NJ, USA. All other chemicals were of reagent grade.

Preparation of Theophylline Coated Tablets

Theophylline, 200 mg, core tablets were prepared by direct compression process using Avicel pH-102 as a direct compressible diluent with magnesium stearate and talcum as lubricant and glidant,

respectively. Chitosan, 0.5% w/w, was dissolved in 1% v/v aqueous acetic acid as a film-coating solution without any plasticizers. The film was coated on the core tablets using a film-coating machine (Rama Coater 18, Narong Karnchang, Thailand) with an air atomizer under the following conditions: spraying rate 15–30 mL/min, pan speed 9 rpm, and drying temperature 55–60°C. The core and coated tablets had been cured at 40, 60, and 100°C for 6, 12, and 24 hr.

Morphology Study

The morphology of the edge and surface of theophylline coated tablets was observed under a scanning electron microscope (model JSM 5800 LV, Jeol, Tokyo, Japan). The samples were attached to the slab surface with double-sided adhesive tape and then coated with gold to a thickness of about 30 nm under vacuum to make the samples conductive. Scanning electron photomicrographs were taken at 150× and 300× magnification.

Fourier Transform Infrared Spectroscopy Study

Chitosan films were prepared from H-type chitosan by the solvent casting technique using 1% v/v acetic acid as solvent. Transmission infrared spectra of the films cured at 40, 60, and 100°C for 24 hr, chitin, and chitosan powder were measured using a Fourier transform infrared (FTIR) spectrophotometer (model Magna-IR™ system 750, Nicolet, WI, USA). The powders were measured by KBr method and the films were measured directly for FTIR spectra.

Solid-State ^{13}C NMR Spectroscopy Study

Carbon-13 NMR spectra of the non-cured chitosan cast film, the chitosan cast films cured at 40, 60, and 100°C for 24 hr, chitin, and chitosan powder were measured using a high resolution solid-state ^{13}C NMR spectrometer (model DPX 300, Bruker, Switzerland).

Tablet Disintegration Study

Tablet disintegration of theophylline non-cured core tablets, core and coated tablets cured at 40, 60, and 100°C for 24 hr, and non-cured coated tablets was investigated in distilled water at 37 ± 2°C using disintegration apparatus (Sotax DT 3, Switzerland).

In Vitro Drug Release Study

The drug release from theophylline non-cured core and coated tablets, core and coated tablets cured at 40, 60, and 100°C for 6, 12, and 24 hr, respectively was investigated in distilled water using USP dissolution apparatus II (Pharmatest, Germany). The paddle speed was 50 rpm and the medium temperature was controlled at 37 ± 0.5°C. In addition, the drug release from non-cured coated tablets and coated tablets cured at 40, 60, and 100°C for 24 hr was also investigated in 0.1 N hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer under the same conditions as the drug release study in distilled water. Theophylline was analyzed using an ultraviolet (UV) spectrophotometer (Perkin Elmer, Lambda 2, USA). The analytical wavelength was 272 nm in distilled water, 270 nm in 0.1 N hydrochloric acid, and 271 nm in pH 4.5 acetate buffer and pH 6.8 phosphate buffer. All the experiments were done in six determinations.

RESULTS AND DISCUSSION

Morphology Study

The average weight gain and film thickness of the theophylline coated tablets were 0.012 g. ($n = 20$) and 0.165 mm ($n = 10$), respectively. Scanning electron photomicrographs of the edge and surface of the non-cured and 24 hr-cured at 40, 60, and 100°C coated tablets are illustrated in Fig. 1. Film cracking at the edge and surface of the coated tablets was observed in all cured tablets. It seemed that the cracking was increased and clearly seen in the tablet cured at 100°C. The increase of film cracking was due to moisture loss during increased curing temperature. It indicated the heat effect on the physical change of chitosan film.

FTIR Spectroscopy Study

Fourier transform infrared spectra of chitin and chitosan powder, non-cured and 24 hr-cured at 40, 60, and 100°C chitosan cast films are shown in Fig. 2. The transmission infrared spectra of all samples exhibited broad peaks in the range of 3448–3365 cm^{-1}. The peaks were assigned to an

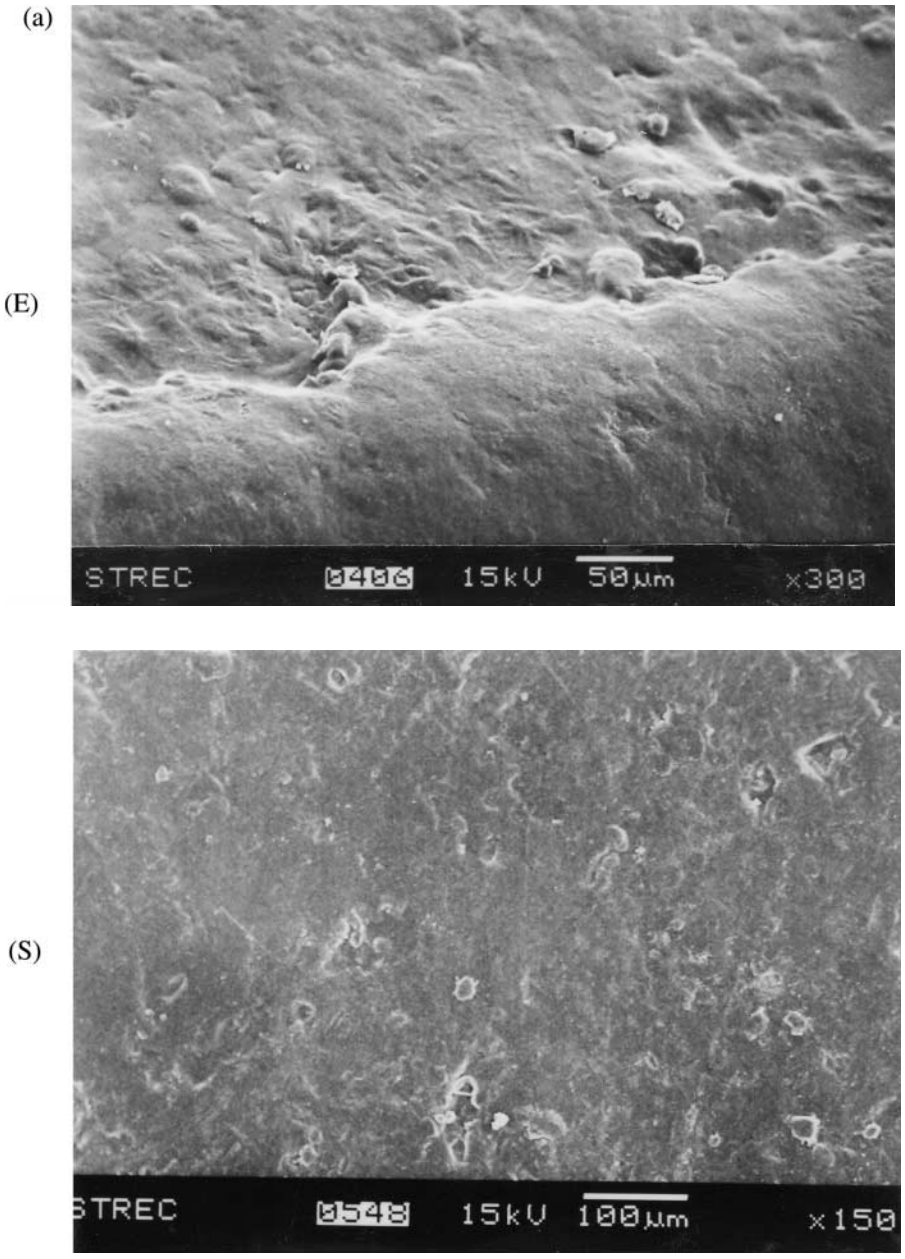

Figure 1. Scanning electron photomicrographs of the edge (E), at magnification of 300×, and surface (S), at magnification of 150×, of non-cured and 24 hr-cured theophylline coated tablets: (a) non-cured, (b) cured at 40°C, (c) cured at 60°C, and (d) cured at 100°C.

(continued)

O–H stretch, indicating intermolecular hydrogen bonding between molecules of chitin/chitosan, and also overlapped in the same region as an N–H stretch.[17,18] The peaks attributed to the C=O stretch (amide I) at 1656 cm^{-1} and the N–H bend (amide II) at 1566 cm^{-1} were observed in the IR spectrum of chitin powder. In the IR spectrum of chitosan powder, the peaks assigned to the NH_2 stretch at 1598 cm^{-1} and the C=O stretch (amide I) at 1658 cm^{-1} were observed, since the H-type chitosan had 80–85% degree of deacetylation and still had an acetylamide functional group in the chitosan

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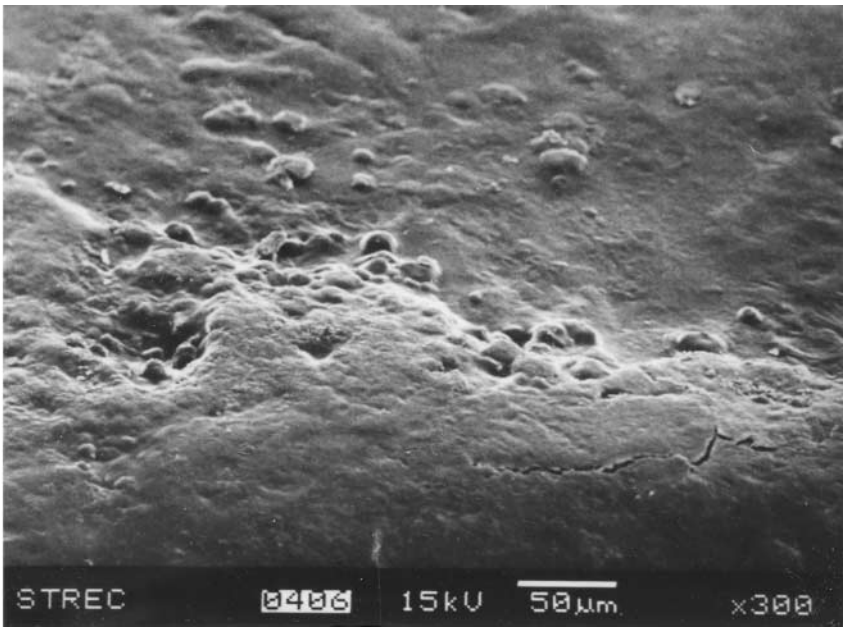
(b)

(E)



(S)

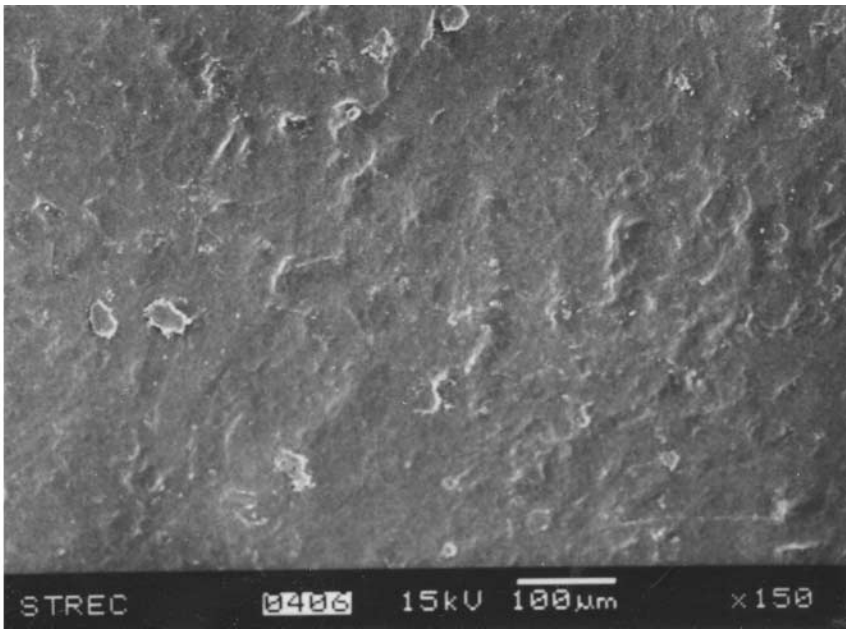


Figure 1. Continued.

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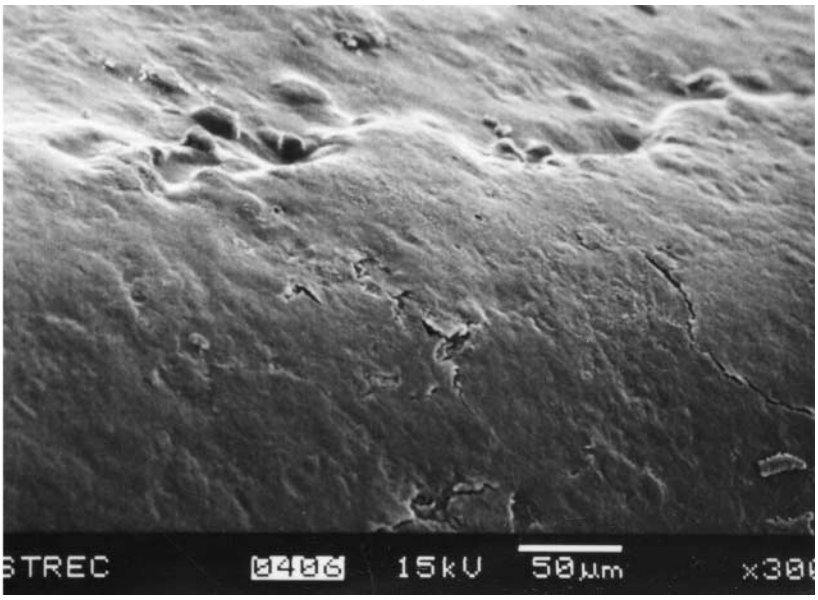
molecule. The strong peak near 1560 cm^{-1} and the weak peak at 1410 cm^{-1} in all spectra of non-cured and cured chitosan films were assigned to an asymmetric and a symmetric carboxylate anion stretch, respectively. The peak attributed to the CO stretch at 1654–1641 cm^{-1} was also observed. It indicated that chitosan films prepared using acetic acid as dissolving vehicle were chitosonium acetate films.[14] The transmission infrared spectra of all cured chitosan films were similar to the non-cured one, and showed no change of IR peaks.

(c)

(E)



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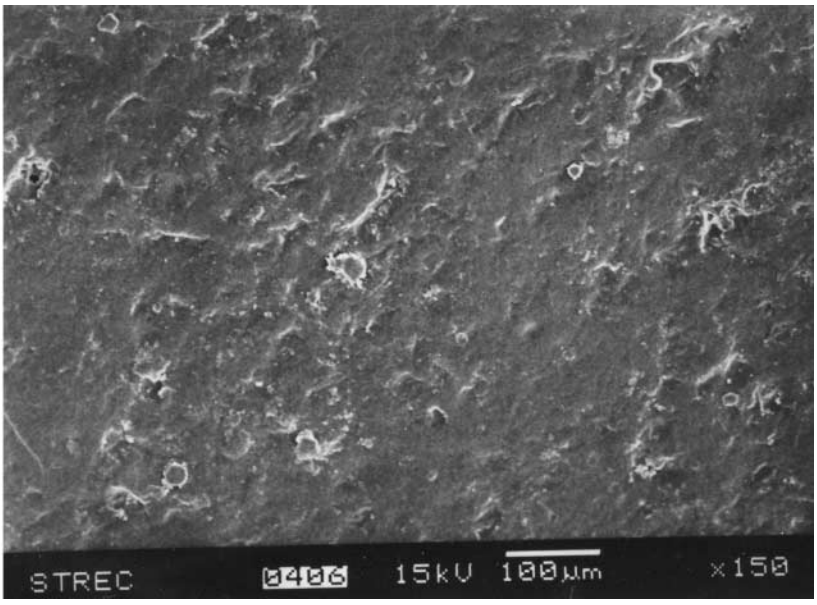


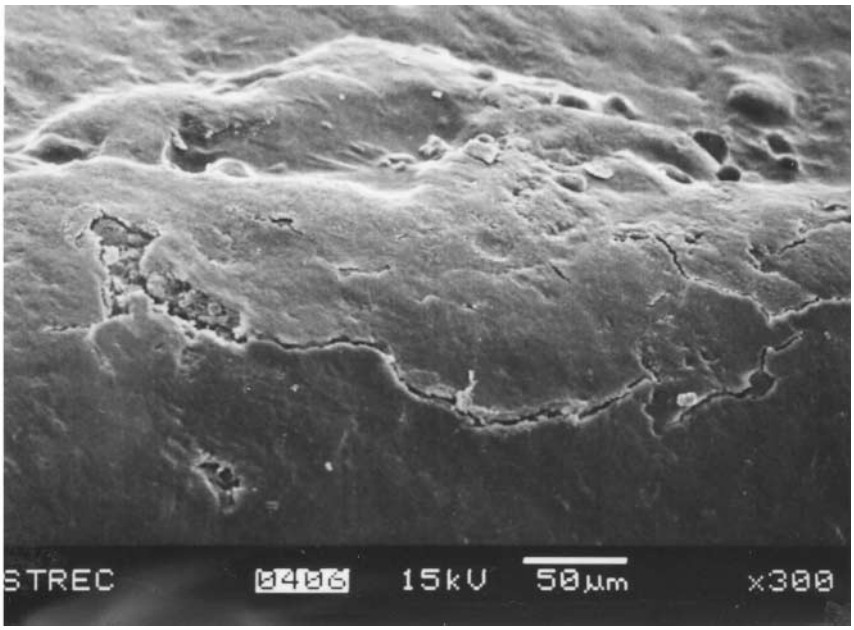
Figure 1. Continued.

Solid-State ^{13}C NMR Spectroscopy Study

Carbon-13 NMR spectra of chitin and chitosan powder, non-cured and 24 hr-cured at 40, 60, and 100°C chitosan cast films are shown in Fig. 3. The resonances at 173 ppm (peak area, 0.464) and 174 ppm (peak area, 0.033) assigned to amide carbonyl carbons were observed in the spectra of chitin and chitosan powder, respectively. In the spectrum of non-cured chitosan film, the resonances around 174 ppm (peak area, 0.075) and 180 ppm assigned to a carbonyl carbon of a chitosonium acetate functional group were observed.[14] When chitosan films had been cured at 40, 60, and 100°C

(d)

(E)



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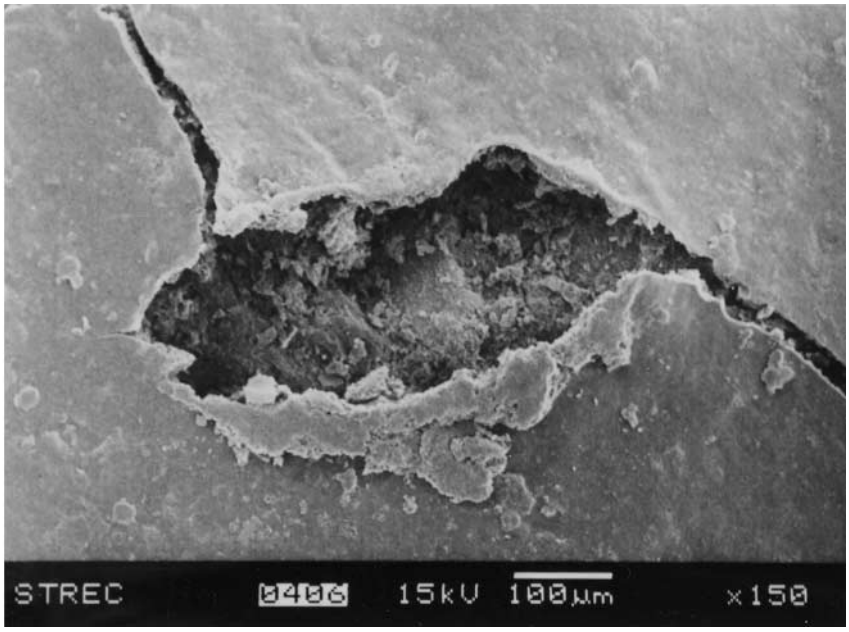

Figure 1. Continued.

for 24 hr, the resonances around 174 ppm with peak area 0.153, 0.170, and 0.194, respectively, were observed. As the curing temperature increased, the peak area assigned to an acetyl amide functional group increased. It exhibited the conversion of chitosonium acetate to acetyl amide form under increasing temperature. Toffey et al.[15] reported the partial conversion of solid-state ^{13}C NMR spectra of chitosonium acetate to chitin, an amidization process, when the film was cured at 100°C for 12 hr. Absolute conversion was observed at a curing temperature of 120°C for 12 hr. They also studied the

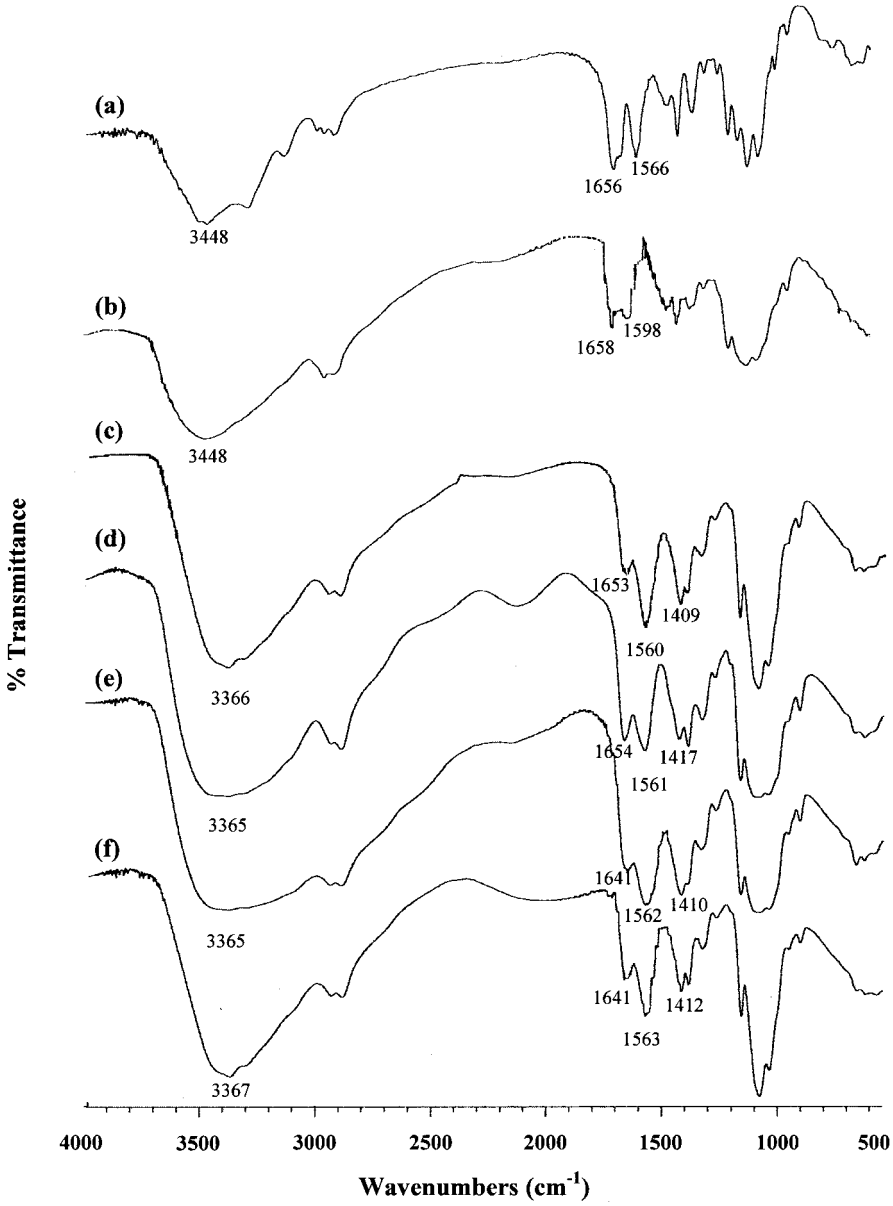

Figure 2. Transmission infrared spectra of (a) chitin powder, (b) chitosan powder, (c) chitosan film, (d) 24 hr-cured chitosan film at 40°C, (e) 24 hr-cured chitosan film at 60°C, and (f) 24 hr-cured chitosan film at 100°C.

thermal behavior of chitosonium acetate films under isothermal curing temperature 80–140°C, and found that the rise in glass transition temperature, T_g, was not due to the loss of residual moisture in the films but the conversion of chitosonium acetate to chitin. Our study of solid-state ^{13}C NMR spectroscopy indicated the heat effect on chemical change of chitosan films.

Tablet Disintegration Study

Tablet disintegration of theophylline non-cured core and coated tablets, theophylline core and coated tablets cured at 40, 60, and 100°C for 24 hr in distilled water is demonstrated in Table 1. The disintegration of all non-cured and cured core tablets was very rapid, with disintegration time less

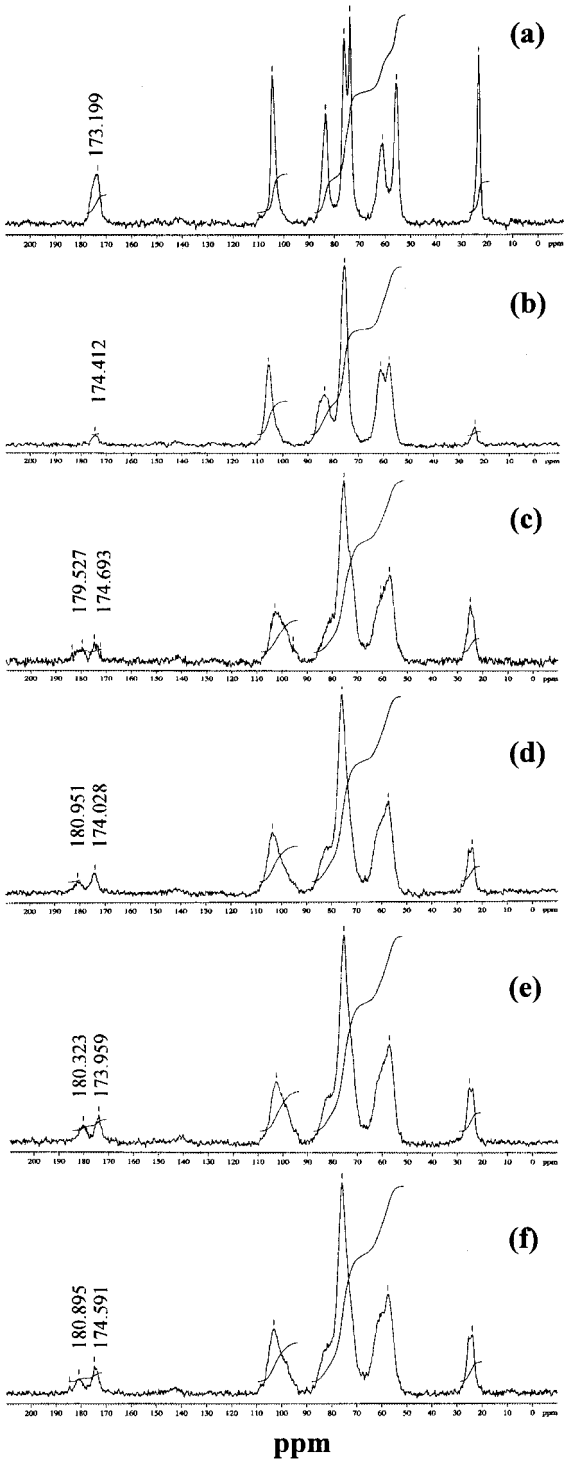

Figure 3. Solid-state ^{13}C NMR spectra of (a) chitin powder, (b) chitosan powder, (c) chitosan film, (d) 24 hr-cured chitosan film at 40°C, (e) 24 hr-cured chitosan film at 60°C, and (f) 24 hr-cured chitosan film at 100°C.

Table 1

Tablet Disintegration of Theophylline Non-cured Core and Coated Tablets, and 24 Hr-Cured Core and Coated Tablets at 40, 60, and 100°C

	Disintegration Time ($n=6$)[a]	
Cured Condition	Core Tablets	Coated Tablets
Non-cured	< 20 sec	> 30.00 min
Cured at 40°C for 24 hr	< 20 sec	> 30.00 min
Cured at 60°C for 24 hr	< 20 sec	> 30.00 min
Cured at 100°C for 24 hr	< 20 sec	10.28±0.04 min

[a]All values are the mean±SD of six samples.

than 20 sec. In theophylline coated tablets, the disintegration time of the non-cured tablets was more than 30 min according to the slow dissolution rate of high molecular weight chitosan films in water.[14] The decrease in disintegration time of the cured coated tablets was observed, especially in the 24 hr-cured tablet at 100°C. This might be due to the effect of heat on film cracking.

In Vitro Drug Release Study

The drug release profiles of theophylline from core and coated tablets in distilled water are shown in Fig. 4. The drug release from the non-cured core tablets was fast release and reached more than 85% within 45 min. The pattern of drug release from the non-cured coated tablets was sustained release. Only 50% of the drug was released within 12 hr. This was due to the slow disintegration rate as well as the slow dissolution rate of high molecular weight chitosan films, as mentioned before.

In curing processes, the release profiles of theophylline from the non-cured and 24 hr-cured coated tablets at 40, 60, and 100°C, respectively, in distilled water are illustrated in Fig. 5. The curing temperature affected the drug release behavior of the coated tablets. Being cured at 100°C, the drug release from the coated tablets was fastest and reached more than 90% within 4 hr, while that of the tablets cured at 40 and 60°C showed sustained release, with a maximum release of 50% and 60% within 12 hr, respectively. This indicated that the curing process at 40 and 60°C had no effect on the drug release

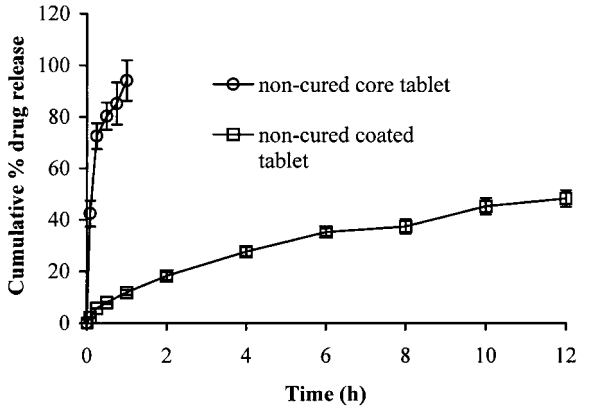

Figure 4. The drug release profiles of theophylline from the non-cured core and coated tablets in distilled water. Data represents the mean±SD of six determinations ($n = 6$).

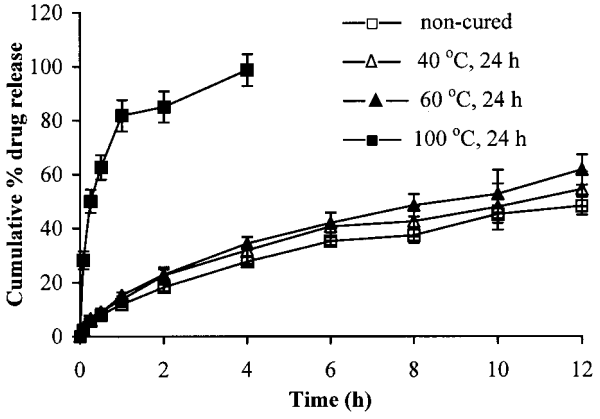

Figure 5. The drug release profiles of theophylline from the non-cured and 24 hr-cured coated tablets at 40, 60, and 100°C, respectively, in distilled water. Data represents the mean±SD of six determinations ($n = 6$).

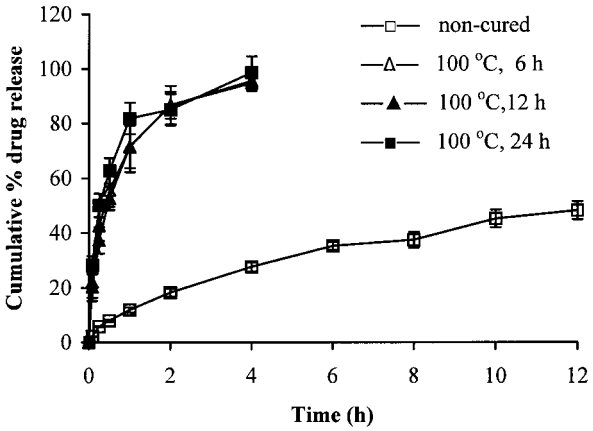

Figure 6. The drug release profiles of theophylline from the non-cured and 24 hr-cured coated tablets at 100°C for 6, 12, and 24 hr, respectively, in distilled water. Data represents the mean±SD of six determinations ($n = 6$).

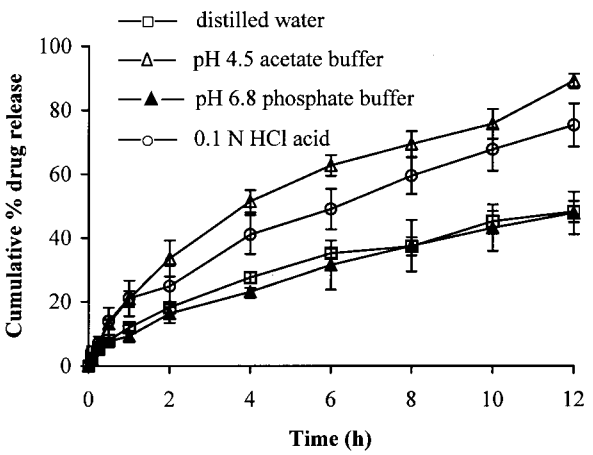

Figure 7. The drug release profiles of theophylline from the non-cured coated tablets in various media. Data represents the mean±SD of six determinations ($n = 6$).

behavior. The fast release pattern of the coated tablets cured at 100°C might be attributed to the greater physical change of the coated film. Though the partial conversion of chitosonium acetate to chitin was observed in ^{13}C NMR spectra of the cured film, and was consistent with Toffey et al.'s study,[15] it had no effect on the drug release behavior of the cured coated tablets. In addition, the effect of curing time on the drug release from theophylline coated tablets cured at 40, 60, and 100°C for 6, 12, and 24 hr was also investigated. As shown in Fig. 6, the drug release behavior of the coated tablets cured at 100°C at any curing time was no different. Similar results were also obtained in those tablets cured at 40 and 60°C (data not shown). This indicates that the curing time had no effect on the drug release behavior.

The drug release profiles of theophylline non-cured coated tablets in various media, i.e., distilled water, 0.1 N hydrochloric acid, pH 4.5 acetate buffer, and pH 7.4 phosphate buffer, are shown in Fig. 7. It was found that the drug release patterns in all media were sustained release. The greatest release was observed when pH 4.5 acetate buffer

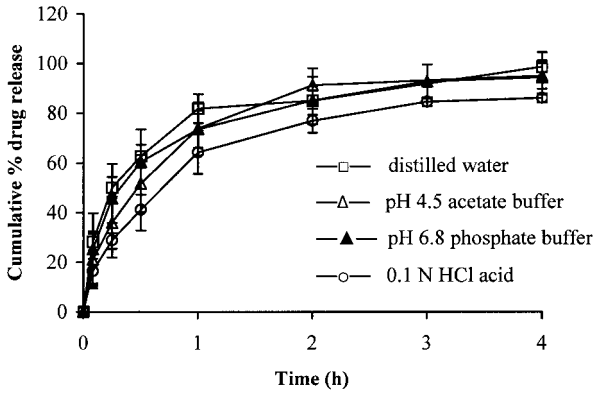

Figure 8. The drug release profiles of theophylline from the 24 hr-cured coated tablets cured in various media. Data represents the mean±SD of six determinations ($n = 6$).

and 0.1 N hydrochloric acid were used as dissolution media. This was due to the greater dissolution of chitosan films in both media.[1,4–6,14] In addition, the drug release behavior of the coated tablets cured at 100°C for 24 hr in all media was changed, as shown in Fig. 8. The fast drug release profiles, which reached 85–90% within 4 hr were observed in all media. It was confirmed that the physical change of chitosan film caused by curing played an important role in the drug release behavior of theophylline coated tablets.

CONCLUSION

The heat effect on the physicochemical characteristics of chitosan films coated on theophylline tablets played an important role in both the physical and chemical change of the film characteristics. The drug release from the film-coated tablets was increased and gave a faster release pattern due to the increase in film cracking induced by heat. The evidence of the heat-induced change in chemical structure of chitosan films was found in the ^{13}C NMR spectra. The partial conversion of chitosonium acetate to chitin was observed, but it had no effect on the drug release behavior. In addition, the film-coating temperature of 55–60°C and the curing process at 40 and 60°C had no effect on the drug release from theophylline tablets coated with chitosan polymer. Finally, chitosan polymer gave appropriate film characteristics for sustained-release coating in all pH range media, and further studies on the development of film formulation and stability are suggested.

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