International Journal of Pharmaceutics 383 (2010) 255–263

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Practical application to time indicator of a novel white film formed by interaction of calcium salts with hydroxypropyl methylcellulose

Sumihiro Shiraishi[a], Yukoh Sakata[b,*], Hiroyuki Yamaguchi[b]

[a] *Research & Development Dept, Qualicaps Co., Ltd., 321-5 Ikezawacho, Yamatokoriyama, Nara 639-1032, Japan*
[b] *Healthcare Research Institute, Wakunaga Pharmaceutical Co., Ltd., 1624 Shimokotachi, Kodacho, Akitakatashi, Hiroshima 739-1195, Japan*

ARTICLE INFO

Article history:
Received 9 July 2009
Accepted 14 September 2009
Available online 18 September 2009

Keywords:
HPMC
Calcium salts
Interaction
White film
Time indicator

ABSTRACT

We have found that a cast film forms a white film when an aqueous solution comprising hydroxypropyl methylcellulose (HPMC) and calcium salts such as calcium lactate pentahydrate (CLP) and calcium chloride ($CaCl_2$) is used. In contrast, the obtained white film was transformed into a transparent film by the addition of purified water. The transformation time for the change from the white film to the transparent film was dependent on film thickness. The relationship between the transformation time and the film thickness was significantly correlated, and it was found that the white film could be adaptable as time indicator. The formation of a white film comprising HPMC and calcium salts was strongly dependent on temperature conditions. The objective of the present study is to investigate the mechanism of the formation of this white film because of the interaction between HPMC and calcium salts. The DSC and XRPD results indicate that the calcium salts affect the HPMC polymer phase in the cast film comprising HPMC and calcium salts. By carrying out attenuated total reflection Fourier transform infrared (ATR FT-IR) analysis, we found that the white film could be formed by the calcium salts affecting the region associated with the C–O–C, C–O, and CH_3 stretching of the HPMC polymer phase.

1. Introduction

Cellulosic polymers have been attracting attention because of their natural reproducibility and high biodegradability. They are primarily used for pharmaceutical coating as they have good film-forming properties that enable the production of a tough coat, protection against photolytic degradation and moisture, prevention of changes in the tablet shape, and masking of the bitter taste of the tablet formulation (Poter, 1989; O'Donnell and McGinity, 2000). Cellulosic polymers, especially hydroxypropyl methylcellulose (HPMC), are universally applicable as a pharmaceutical coating because they are non-ionic and highly soluble.

Most of the additives incorporated in protective films are usually plasticizers, pigments, or other film-forming polymers. Okhamafe and Iwebor (1986) have reported that the highly water-soluble additives, citric acid and urea, affect the moisture permeability of films that are made of HPMC and polyvinyl alcohol (PVA). Okhamafe and York (1988, 1989) have also reported that small amounts of ephedrine hydrochloride have a plasticizing effect on both HPMC and PVA films. The nature and degree of excipient/polymer interactions exert a significant influence on film properties.

In a previous study, we reported that a cast film forms a white film when an aqueous solution consisting of HPMC and calcium salts, such as calcium lactate pentahydrate (CLP) or calcium gluconate, is used (Sakata et al., 2006). CLP is one of the most important sources of calcium, and in comparison with other organic calcium salts, has good solubility and bioavailability. Bolhuis et al. (2001) have reported that CLP has an important function as a filler–binder for the direct compaction of tablets. Hattori et al. (1998a,b,c) have reported that aqueous $Ca(SCN)_2$ solution capable of dissolving cellulose may form a stable complex-like structure with cellulose. Thus, calcium plays an important role in the functionality of cellulose films.

Thus far, a white film composed of HPMC has been formed using a combination of titanium dioxide (TiO_2). TiO_2 is a pigment that is often included in the outer film as an agent that protects against photolytic degradation (Bechard et al., 1992) and masks the tablet surface but which affects the physical properties of the film, such as strength and flexibility, and the disintegration behaviour of the coated tablet. In contrast, it is well known that TiO_2 is a strong photocatalyst, inducing an oxidation–reduction reaction at the solid contact interface or close interface between solids because of certain types of free radicals. Kakinoki et al. (2004) have reported that famotidine is stable against irradiation without TiO_2, whereas it exhibits marked discoloration in the presence of TiO_2. This discoloration is significantly dependent on both the irradiation wavelength and the crystal form of TiO_2 at high humidity. As

---

* Corresponding author. Tel.: +81 826 45 2331; fax: +81 826 45 4351.
E-mail address: sakata_y@wakunaga.co.jp (Y. Sakata).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.09.024

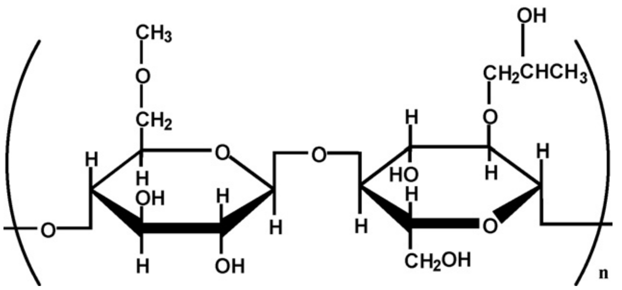

Fig. 1. Chemical structure of HPMC.

the crystal form of TiO_2, two types of rutile and anatase are useful for pharmaceutical coating. Recently, the anatase forms have been manufactured extensively instead of the rutile forms because the photocatalyst behaviour of the anatase forms is stronger than that of the rutile forms. Thus, the white film containing TiO_2 is associated with various problems.

In order to avoid the various problems due to TiO_2, we demonstrated the application of the white film consisting of HPMC and CLP for pharmaceutical coating (Sakata et al., 2006). Further, we found that the white films consisting of HPMC and calcium salts, such as CLP and $CaCl_2$, were applicable to time indicator. However, the formation of the white films was strongly dependent on the drying temperatures during the film formation process. In addition, the preparation temperature of the white film was different in the case of CLP from that in the case of $CaCl_2$. Therefore, the present study was conducted to evaluate the function of CLP and $CaCl_2$ in the films that were formed by the interaction between HPMC and calcium salts (CLP and $CaCl_2$), and to investigate the mechanism of the formation of white films.

2. Experimental

2.1. Materials

Hydroxypropyl methylcellulose (HPMC: TC-5R) was purchased from Shinetsu Chemical Co., Ltd., Japan. Calcium lactate pentahydrate (CLP) was purchased from Komatsuya Chemical Co., Ltd., Japan. Calcium chloride ($CaCl_2$) was purchased from Tomita Pharmaceutical Co., Ltd., Japan. The structures of HPMC are shown in Fig. 1.

2.2. Preparation of HPMC solutions and that of film of time indicator

20 g of CLP or $CaCl_2$ was dissolved in 830 g of distilled water that was heated to approximately 80 °C, and 150 g of HPMC was added thereto while stirring to prepare suspensions. The resulting suspensions were dissolved by stirring at a temperature of 50 °C or lower, degassed under reduced pressure, and allowed to stand at room temperature (RT) for 12 h in order to obtain clear HPMC gels. By using an apparatus for thin-layer chromatography, we cast the HPMC gel on a glass plate to form a thin HPMC gel film and then dried it at RT for 12 h or 80–120 °C for 1 h in order to form a film. The cast films were used as samples for DSC, XRPD, and ATR FT-IR analysis. In addition, several films having different thicknesses were prepared in the same manner.

2.3. Differential scanning calorimetry analysis

A thermal analysis of the samples was performed with a differential scanning calorimeter (DSC EXSTRA 6000 with a DSC 30E measuring cell; Seiko). Approximately 5 mg of a sample was weighed into the DSC pan, and the sealed pan was placed in the sample side of the instrument. An identical reference pan was placed in the reference side. Scans were carried out at a rate of 10 °C/min at temperatures of between 25 °C and 250 °C, using a nitrogen gas purge at 50 ml/min.

2.4. X-ray powder diffraction (XRPD) analysis

XRPD analysis was carried out at room temperature with a type Rint2550VHF diffractometer (Rigaku, Tokyo, Japan). Measurement conditions were as follows: target, copper; filter, Kα; voltage, 40 kV; current, 450 mA; time constant, 1 s; step slit, 1.0°; counting time, 1.0 s; measurement range, $2\theta = 2.5–60°$.

2.5. Attenuated total reflection Fourier transform infrared (ATR FT-IR) spectroscopy

Each sample was analysed in an ATR FT-IR spectrometer (FT-IR-620, Jasco, Tokyo, Japan) equipped with a deuterated L-alanine triglycine sulphate (DLATGS) detector. The sample film was placed in a horizontal ATR accessory (Pike Tech., WI, USA) with a zinc selenide prism for the analysis. All spectra were obtained through 52 scans at a resolution of 4 cm^{-1} at ambient temperature (25 °C). Three batches of each sample film were analysed. The individual spectrum of three analyses of each sample was obtained and averaged to produce a single spectrum for subsequent data processing. Spectral Manager for Windows software (Jasco, Tokyo, Japan) was used for data acquisition and holding.

3. Results and discussion

3.1. Formation and characterization of a white film consisting of HPMC and calcium salts

In a previous study, we reported that solutions consisting of HPMC and calcium salts could be used for forming a white film. However, no report describes the preparation conditions required to obtain the white film. It is predicted in the following study that the drying temperature for the film preparation may be as important a factor for the formation of a white film as the presence of Ca ions. Various cast films were prepared from HPMC jelly containing Ca ions and from HPMC jelly with no ions. All transparent films were formed from a jelly consisting of HPMC regardless of the drying temperature, as shown in Fig. 2(a)–(c). When dried at 80 °C, the clear jelly containing CLP changed into a white film, as shown in Fig. 2(e). However, when the jelly was dried at 25 °C, a transparent film was formed, as shown in Fig. 2(d). Moreover, as shown in Fig. 2(f), when the jelly was dried at 120 °C, the film finally became transparent in spite of the formation of a white film during the drying process.

In contrast, the jelly containing $CaCl_2$ formed a white film when dried at 80 °C and 120 °C but not when dried at 25 °C, as shown in Fig. 2(g)–(i). These results suggest that the type of Ca salt affects the formation of the white film in the same was as the drying temperature.

Moreover, to verify the above-mentioned conclusion, we investigated the detailed temperatures at which the HPMC jelly changed into a white film. As shown in Fig. 3, white films were perfectly formed by heating at temperatures more than 60 °C although the white part appeared partially on the film at 50 °C. This temperature is similar to that at which the gel formation of HPMC occurs because of heating. Therefore, it was supposed that the gel formation of HPMC may participate in the formation of a white film with Ca ions.

These white films have the characteristic to allow one to visually recognize moisture by changing from a non-transparent colour to

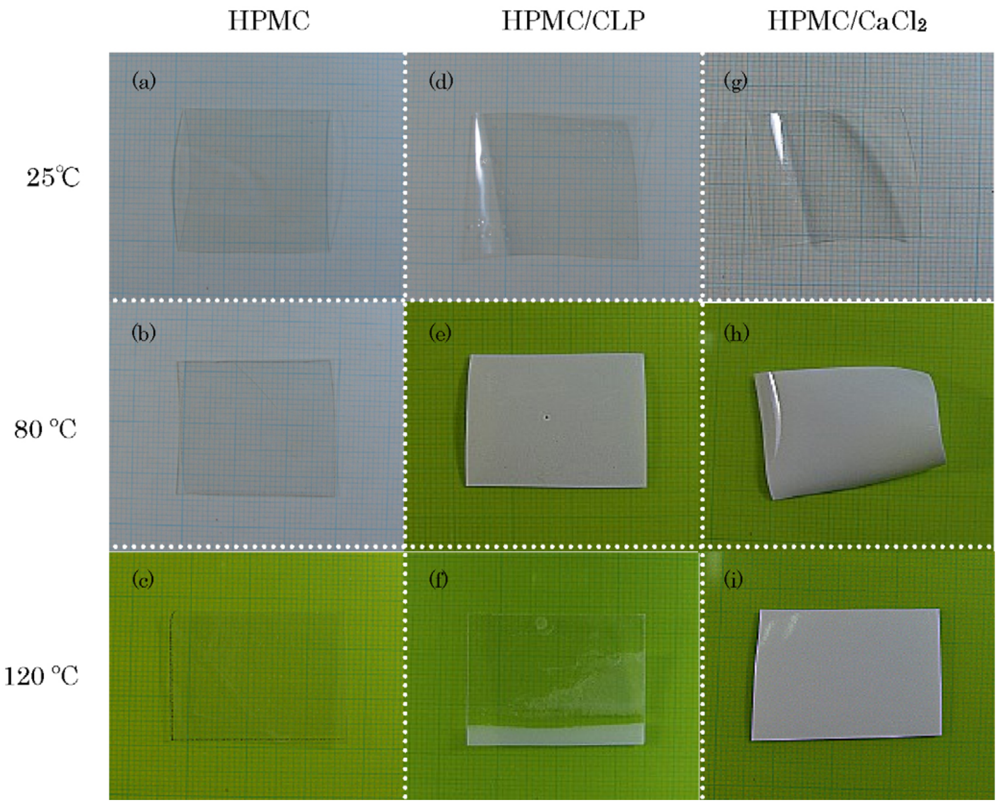

Fig. 2. Photograph of cast film of HPMC and of HPMC and calcium salts prepared at 25 °C, 80 °C, and 120 °C. (a) HPMC only at 25 °C, (b) HPMC only at 80 °C, (c) HPMC only at 120 °C, (d) HPMC/CLP at 25 °C, (e) HPMC/CLP at 80 °C, (f) HPMC/CLP at 120 °C, (g) HPMC/$CaCl_2$ at 25 °C, (h) HPMC/$CaCl_2$ at 80 °C and (i) HPMC/$CaCl_2$ at 120 °C.

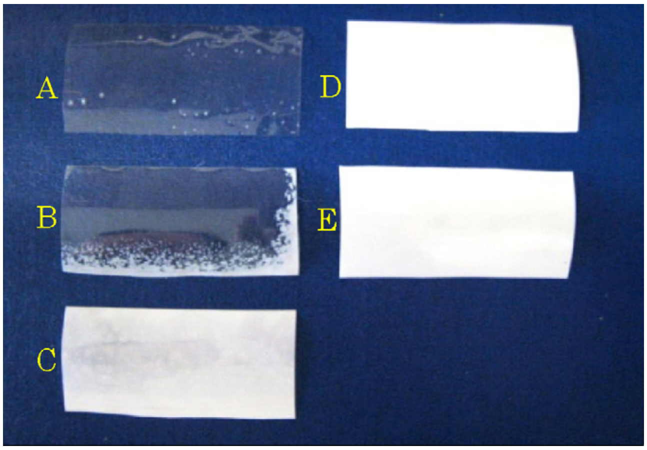

Fig. 3. Effect of drying temperature on the formation of white colour of HPMC film containing CLP. (A) Drying at 25 °C, (B) drying at 50 °C, (C) drying at 60 °C, (D) drying at 70 °C and (E) drying at 80 °C.

transparent when they are moistened, as shown in Fig. 4. This characteristic makes it convenient to adapt a sheet-like time indicator that is different from the conventional white film by using a colour agent such as titanium oxide.

Fig. 5 shows the relationship between the film thickness and the clearing time at which the film changed to transparent after water was dropped on it. The film thickness and the clearing time were correlated well for both the films containing CLP (Fig. 5(a)) or $CaCl_2$ (Fig. 5(b)). These results suggest that an optional time indicator can be designed by controlling the film thickness.

3.2. Interaction between HPMC and calcium salts

Subsequently, to confirm that the formation of the white film was restricted by the interaction of HPMC and calcium salts, XRPD and DSC analysis were performed using the prepared cast film.

Fig. 6 shows the XRPD patterns of cast films that were prepared at different drying temperatures. The cast films prepared with HPMC-only solutions exhibited two broad diffraction pat-

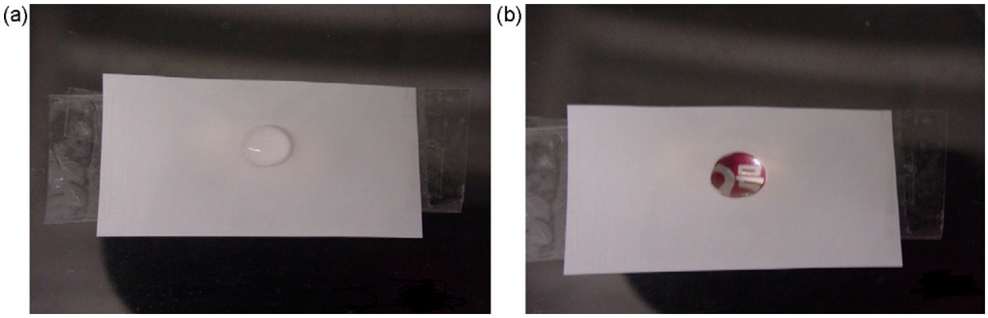

Fig. 4. Photograph of cast film consisting of HPMC/CLP blends before (a) and after (b) water spots.

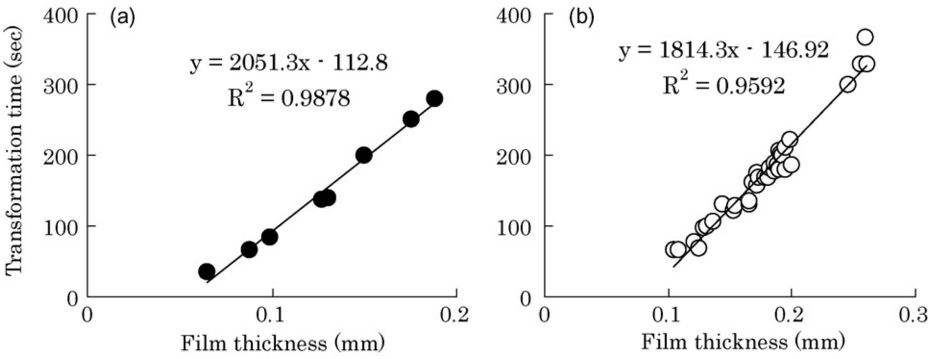

Fig. 5. Relationship between transformation time of white film and film thickness of cast film consisting of HPMC/CLP (a) and of HPMC/$CaCl_2$ (b) blends.

terns. However, the diffraction pattern of the cast films prepared by using only HPMC at 25 °C (Fig. 6(a)) was significantly different from that of films prepared at 80 °C (Fig. 6(b)) and at 120 °C (Fig. 6(c)). Further, the diffraction intensity of the first peak observed in the cast films prepared by using only HPMC increased with an increase in the drying temperature (Fig. 6(a)–(c)). In contrast, the diffraction pattern and the diffraction intensity of HPMC-only films were strongly affected by the addition of calcium salts. The diffraction patterns of cast films consisting of HPMC/CLP blends prepared at 25 °C were similar to those of the HPMC-only films. However, the diffraction patterns of cast films consisting of HPMC/$CaCl_2$ blends prepared at 25 °C were different significantly from those of the HPMC-only films. The diffraction intensity of cast films consisting of HPMC/CLP and HPMC/$CaCl_2$ blends was smaller than that of cast films containing only HPMC. By increasing the drying temperature, we could increase the diffraction intensity of cast films consisting of HPMC/CLP blends. Further, the diffraction pattern and the diffraction intensity of these cast films were similar to those of the HPMC-only films. In contrast, the diffraction intensity of the cast film consisting of HPMC/$CaCl_2$ blends did not change with a change in the drying temperature, whereas the diffraction pattern changed with an increase in the drying temperature. These results suggest that the molecular motion of the HPMC polymer phase would be affected by the addition of calcium salts and by the preparation temperature of the cast film, and no crystalline form was observed for each film.

Fig. 7 shows the DSC profiles of cast films that were prepared at different drying temperatures. The cast films of HPMC-only films exhibited the glass transition temperature (T_g) at 142.2–145.9 °C. As shown in Fig. 6, the HPMC polymer is formed by amorphous areas. Amorphous polymers are thermally characterized by the presence of the T_g, which is the transition point between a highly viscous brittle structure called glassy state and a less viscous, more mobile, rubbery state.

In contrast, T_g is considered to be one of the properties most relevant to the assessment of the practical use of the HPMC polymer. The T_g value of a glassy polymer can be modified by blending it with a small amount of a substance. This phenomenon is called plasticization when it ends up with a decrease in the polymer T_g and an increase in the elastic modules resulting in a higher polymer flexibility or mobility. Conversely, when the T_g is increased by the addition of a substance, the phenomenon is regard as antiplasticization. Therefore, the performance of a polymer can be modified in the presence of a plasticizer, or another substance,

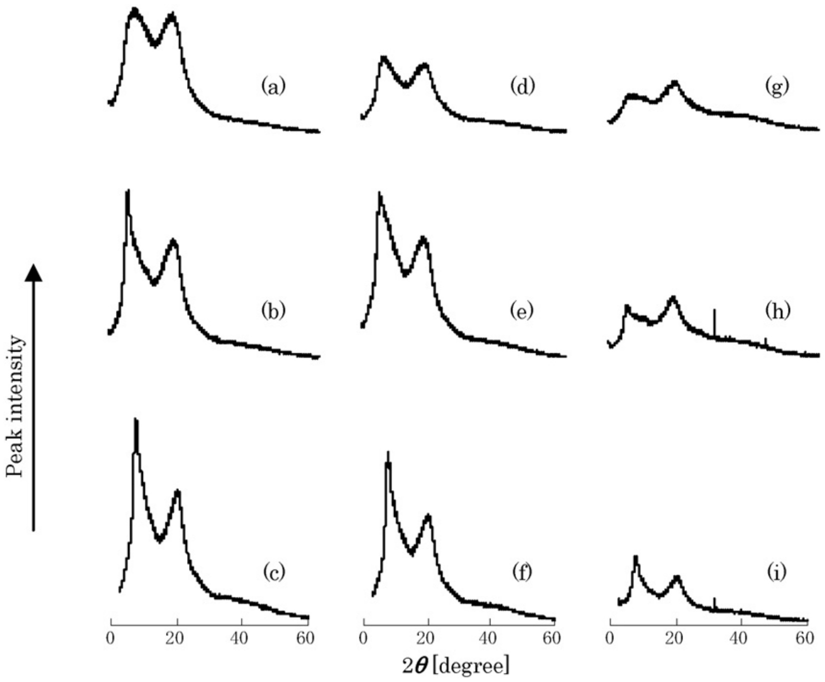

Fig. 6. XRPD patterns of cast film of HPMC and of HPMC and calcium salts prepared at 25 °C, 80 °C, and 120 °C. (a) HPMC only at 25 °C, (b) HPMC only at 80 °C, (c) HPMC only at 120 °C, (d) HPMC/CLP at 25 °C, (e) HPMC/CLP at 80 °C, (f) HPMC/CLP at 120 °C, (g) HPMC/$CaCl_2$ at 25 °C, (h) HPMC/$CaCl_2$ at 80 °C and (i) HPMC/$CaCl_2$ at 120 °C.

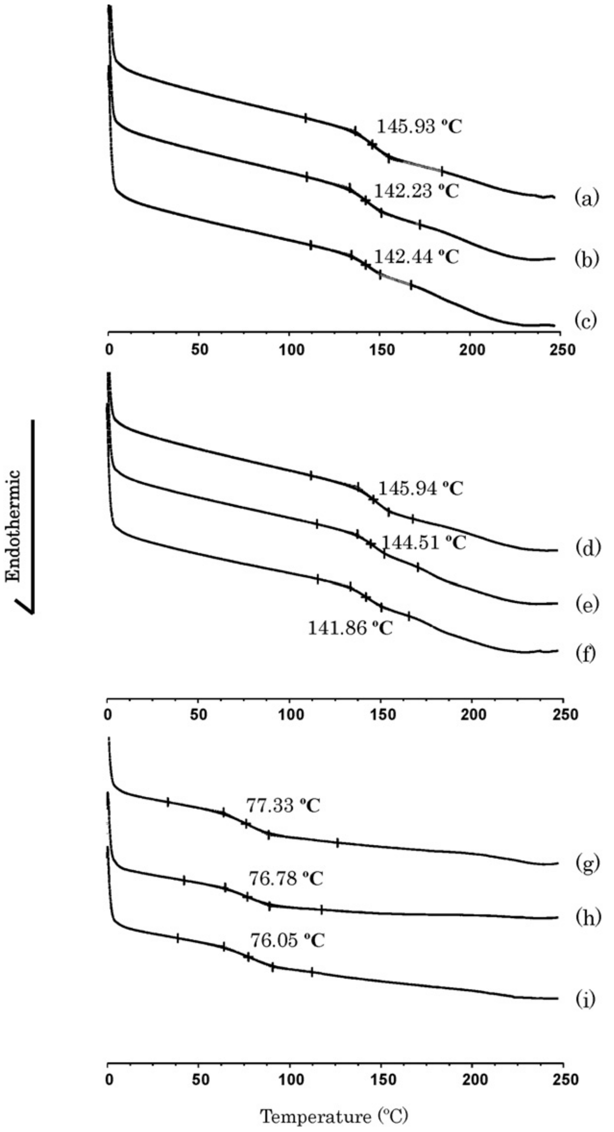

Fig. 7. DSC profiles of cast film of HPMC and of HPMC and calcium salts prepared at 25 °C, 80 °C, and 120 °C. (a) HPMC only at 25 °C, (b) HPMC only at 80 °C, (c) HPMC only at 120 °C, (d) HPMC/CLP at 25 °C, (e) HPMC/CLP at 80 °C, (f) HPMC/CLP at 120 °C, (g) HPMC/$CaCl_2$ at 25 °C, (h) HPMC/$CaCl_2$ at 80 °C and (i) HPMC/$CaCl_2$ at 120 °C.

depending on the nature of the association between the various phases.

In order to study the interaction between HPMC and calcium salts, first, DSC profiles of the cast films consisting of HPMC/CLP blends are shown in Fig. 7(d)–(f). The DSC profiles of the cast films consisting of HPMC/CLP blends were similar to those of the HPMC-only film, which indicated the value of T_g at 141.9–145.9 °C. T_g of the HPMC-only cast film and that of the film consisting of the HPMC/CLP blends were affected by preparation temperatures, which decreased with an increase in the drying temperature. In contrast, DSC profiles of the cast films consisting of HPMC/$CaCl_2$ blends were significantly different from those of the HPMC-only films and of films consisting of the HPMC/CLP blends, which indicated the value of T_g at 76.1–77.3 °C (Fig. 7(g)–(i)). In addition, T_g of the cast films consisting of HPMC/$CaCl_2$ blends increased with an increase in the drying temperature.

In a previous study, we reported that the formation of the white film may be attributable to the interaction between cellulose and calcium ions. Therefore, these results suggest that the molecular motions of amorphous areas in the HPMC polymer was affected by the distribution state and the distribution phase of calcium into cast films, which would be related to the formation of white films due to the interaction between HPMC and calcium salts.

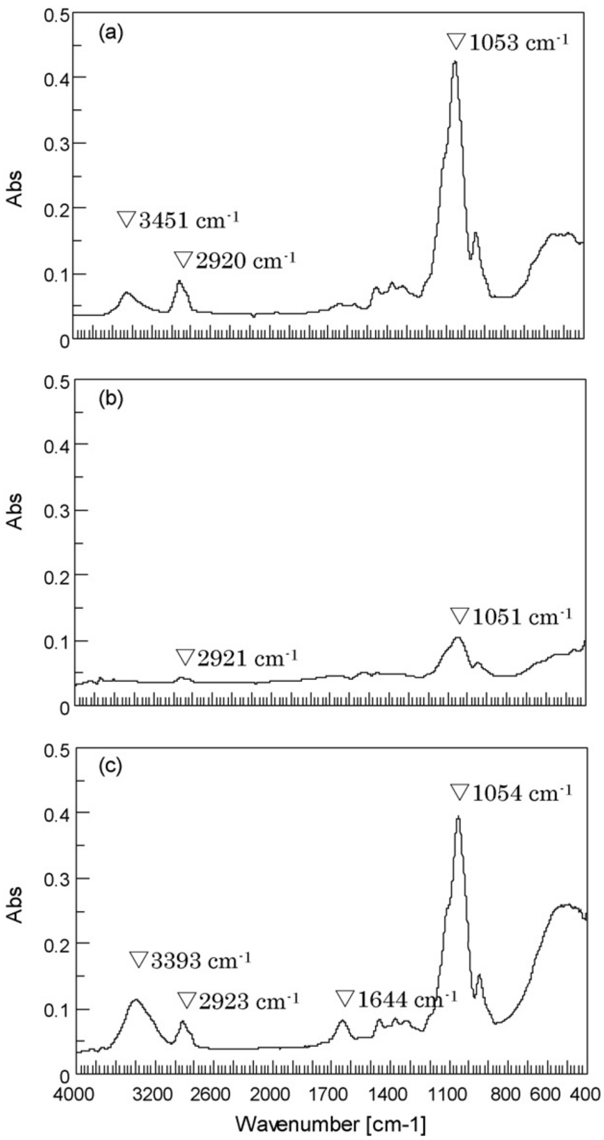

Fig. 8. FT-IR spectra of cast film of HPMC and of HPMC and calcium salts prepared at 25 °C. (a) HPMC, (b) HPMC/CLP and (c) HPMC/$CaCl_2$.

3.3. *Effects of calcium salts and preparation temperature on HPMC polymer phase*

The FT-IR spectroscopy method is a powerful tool used widely for the study of chemical and physical changes in the molecular structure of biological materials. This method has been used for the investigation of the interaction between HPMC and CLP in a sprayed film obtained using various ratios of HPMC and CLP (Sakata et al., 2006). Recently, the ATR FT-IR method is used for molecular motion analysis in solid states. In this section, the effects of calcium salts and preparation temperatures of cast films on the molecular motion of the HPMC polymer phase into cast films consisting of HPMC/calcium salts blends are discussed.

Fig. 8(a) shows the ATR FT-IR spectra of cast films obtained at 25 °C using HPMC-only solutions (15:0%, w/w). The functional groups associated with the HPMC polymer were CH, CH_2, CH_3, C–O–C, C–O, and H–O–H. The assignment of the peaks of the

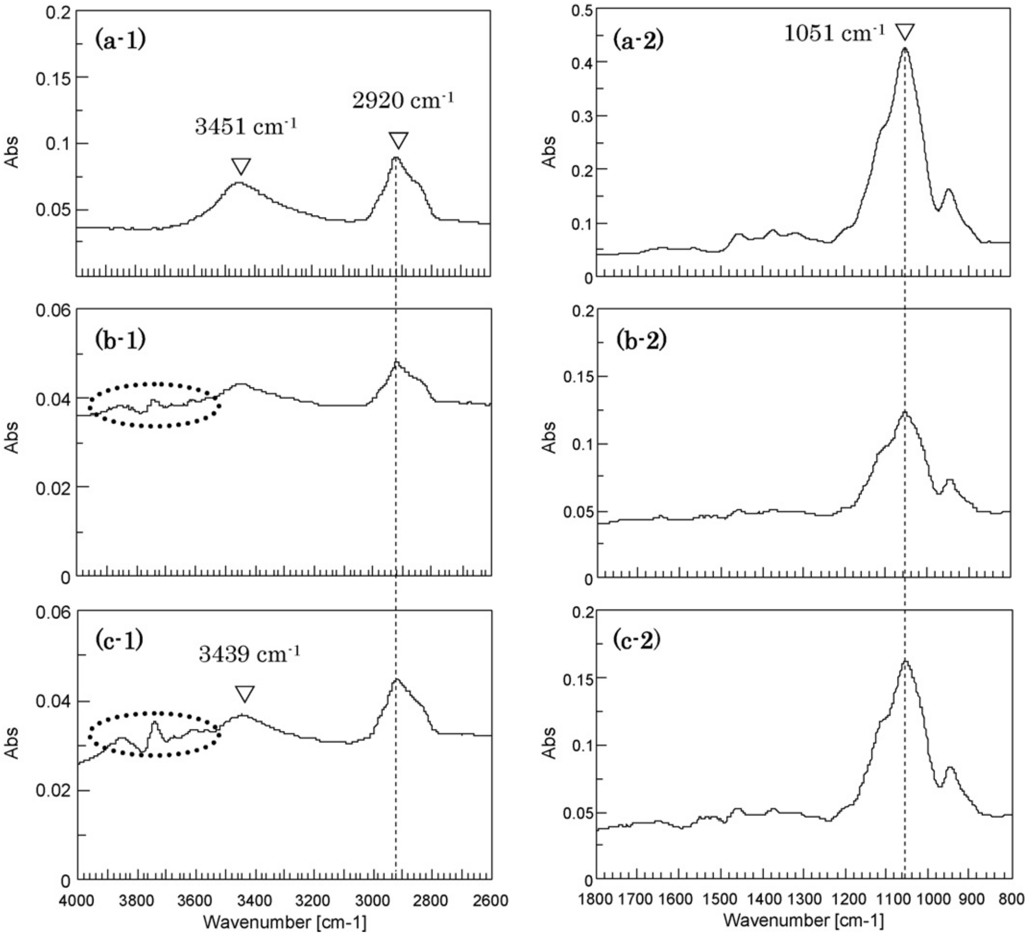

Fig. 9. FT-IR spectra of HPMC films prepared at 25 °C, 80 °C, and 120 °C. (a-1 and a-2): 25 °C, (b-1 and b-2): 80 °C and (c-1 and c-2): 120 °C.

HPMC polymer is as follows: 1250–1460 cm^{-1}, CH, CH_2 stretching; 2850–2980 cm^{-1}, CH_3 stretching; 1000 cm^{-1}, C–O–C, C–O stretching alcohol absorption; 1648 cm^{-1}, absorbed water (H–O–H); broad absorption band at 3500 cm^{-1}, hydrogen bonding in the polymer.

The peaks in the 1250–1460 cm^{-1} and 2850–2980 cm^{-1} region associated with –CH, CH_2, and CH_3 stretching were observed in the 1250–1455 cm^{-1} and 2920 cm^{-1}. The absorption band corresponding to hydrogen bonding was observed at 3451 cm^{-1}. The C–O–C and C–O stretching alcohol absorption bands were observed at 1053 cm^{-1}. However, absorption bands at 1648 cm^{-1} corresponding to absorbed water were not observed.

In contrast, the HPMC polymer phase was significantly changed by the addition of calcium salts such as CLP and $CaCl_2$. Fig. 8(b) shows the ATR FT-IR analysis of cast films obtained at 25 °C using solutions consisting of HPMC/CLP (15:3%, w/w) blends. The peak patterns of their cast film differed significantly from those of HPMC-only films. The stretching region observed in the HPMC polymer phase shifted to a lower field upon the addition of CLP having a concentration of 3% (w/w). In particular, the peak patterns and peak intensity in the 1053 cm^{-1} region that was associated with the C–O–C and C–O stretching of the HPMC polymer phase also shifted to a lower field at 1051 cm^{-1} and decreased significantly by the addition of CLP. Moreover, the peak patterns in the 1250–1455 cm^{-1} and 2920 cm^{-1} regions that were associated with –CH, CH_2, and CH_3 stretching in the polymer were both significantly affected by the addition of CLP. In addition, the peak patterns and the peak intensity in the 3451 cm^{-1} region corresponding to the hydrogen bonding in the polymer were both significantly affected by the addition of CLP.

Fig. 8(c) shows the ATR FT-IR analysis of cast films obtained at 25 °C using solutions consisting of HPMC/$CaCl_2$ (15:3%, w/w) blends. Unlike the ATR FT-IR results of cast films consisting of HPMC/CLP blends, the peak patterns of cast films consisting of HPMC/$CaCl_2$ blends indicated profiles similar to those of the HPMC-only films. However, the peak at 2920 cm^{-1} associated with the CH_3 stretching and that at 3451 cm^{-1} corresponding to the hydrogen bonding of the HPMC polymer phase shifted to 2923 cm^{-1} and 3393 cm^{-1} upon the addition of $CaCl_2$, respectively.

Therefore, the molecular motion in the HPMC polymer phase was affected by calcium salts, and their molecular motions differed significantly from those of the calcium used, whereas the molecular motion of the HPMC-only cast films prepared at 25 °C and that of the films consisting of HPMC and calcium salts indicated that all these films were transparent.

Subsequently, the ATR FT-IR spectra of the cast films prepared at 25 °C, 80 °C, and 120 °C using HPMC-only solutions are shown in Fig. 9. The peak patterns of the cast film were affected strongly by the drying temperature. The peak patterns in the 3451 cm^{-1} region corresponding to the hydrogen bonding in the polymer differed significantly when the drying temperature of the cast films was increased. In particular, the peak patterns at 3451 cm^{-1} corresponding to the hydrogen bonding in the polymer shifted to 3439 cm^{-1} in cast films prepared at 120 °C. In addition, the peak patterns in the 3400–4000 cm^{-1} of the cast films prepared at 25 °C were also changed significantly by the increase in the preparation temperature of the HPMC cast films. In contrast, the peak position at 2920 cm^{-1} corresponding to CH_3 stretching and at 1053 cm^{-1} corresponding to the C–O–C and C–O stretching of the HPMC poly-

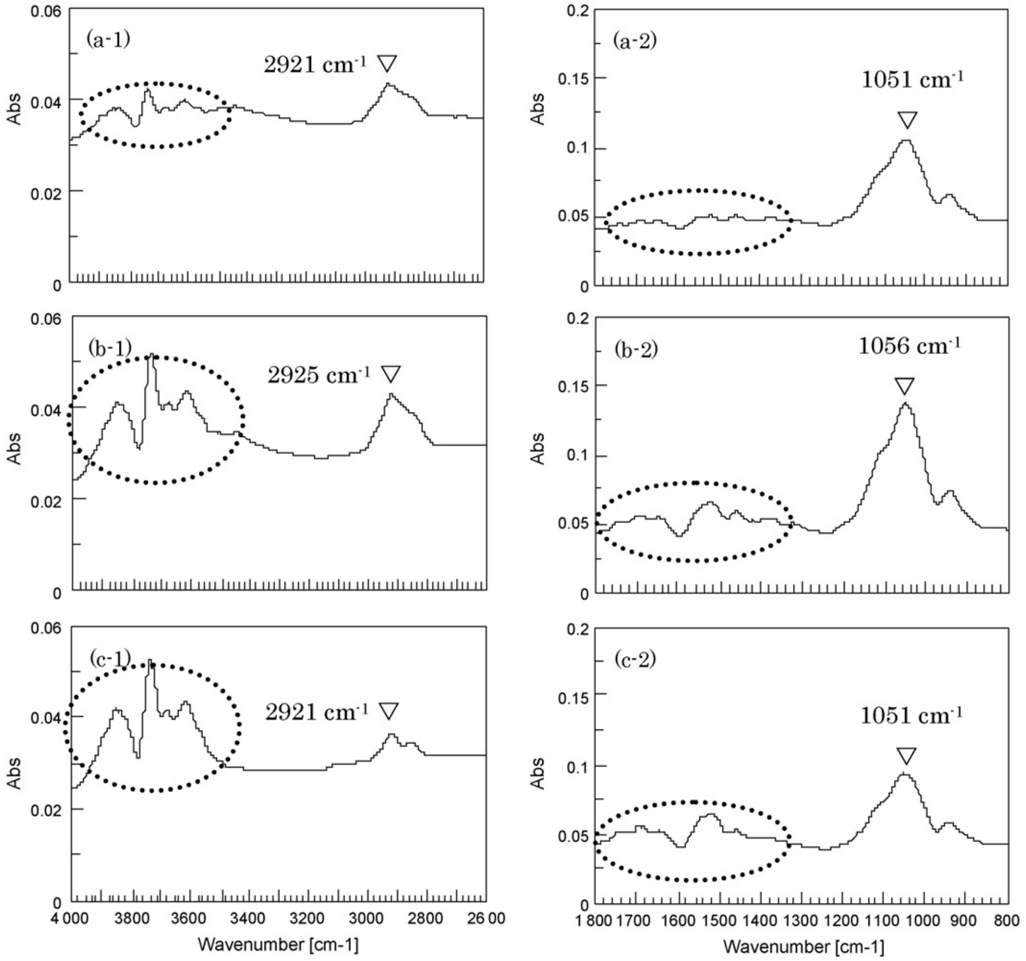

Fig. 10. FT-IR spectra of cast film consisting of HPMC and CLP blends prepared at 25 °C, 80 °C, and 120 °C. (a-1 and a-2): 25 °C, (b-1 and b-2): 80 °C and (c-1 and c-2): 120 °C.

mer phase at 25 °C did not change in the cast films prepared at 80 °C and at 120 °C. Moreover, the peak intensities at 3451 cm^{-1} and 2920 cm^{-1}, and 1053 cm^{-1} in the HPMC polymer phase were decreased, and increased with an increase in the preparation temperature of the cast film, respectively, since the atoms or molecules occupied a fixed site with very little vibrational motion in the solid state.

As shown in Fig. 2, HPMC-only cast films and the cast films consisting of HPMC/calcium salts blend prepared at 25 °C were transparent. The addition of calcium salts affected the molecular motion of the HPMC polymer phase in the low and high fields. Moreover, the molecular motion in the HPMC-only cast film was affected by the increase in the preparation temperature of the cast film, whereas the peak position at 2920 cm^{-1} corresponding to the CH_3 stretching and at 1053 cm^{-1} corresponding to the C–O–C and C–O stretching did not shift.

In contrast, cast films including HPMC and calcium salts formed the white film when the preparation temperatures were increased (Fig. 3). However, the cast films consisting of HPMC and calcium salts did not form the white film upon the addition of PVP (data not shown). Chan et al. (2003) reported that the extent of net reduction between HPMC polymers was attributable to the anti-tack action of PVP. This is because PVP, a well-known hydrogen bond acceptor, is capable of forming hydrogen bonds with HPMC and with water upon dissolving in an aqueous HPMC solution. The PVP molecule contains only a basic carbonyl group capable of donating electrons. Therefore, Chan et al. (2003) have hypothesized that the most likely interaction between HPMC and PVP occurs through hydrogen bonding between oxygen atom and (O (6)) in HPMC and the basic carbonyl group of PVP. Nyamweya and Hong (2000) reported that HPMC and PVP were miscible, as evidenced by a single glass transition temperature. In addition, HPMC and calcium salts indicated a single glass transition temperature, as shown in Fig. 6. The present results suggest that Ca and PVP interact with the same or a similar site of HPMC. Therefore, these results suggest that white film formed from HPMC and calcium salts may be formed through the interaction between CH_3, C–O–C, and C–O in the HPMC polymer phase and ionic Ca.

3.4. Effects of preparation temperature on HPMC polymer phase of cast films consisting of HPMC and calcium salts

In order to confirm the relationship between the formation of the white film and the molecular motion of the HPMC polymer phase, ATR FT-IR analyses of cast films obtained by compounding HPMC/CLP and HPMC/$CaCl_2$ blends under various conditions are performed.

Firstly, the effects of the preparation temperature on the molecular coordination of the HPMC polymer phase in cast films consisting of HPMC/CLP blends are shown in Fig. 10. The peak position at 2921 cm^{-1} corresponding to the CH_3 stretching shifted to 2925 cm^{-1} in cast films prepared at 80 °C, whereas that in the cast film prepared at 120 °C did not shift. Moreover, the peak position at 1051 cm^{-1} corresponding to the C–O–C and C–O stretching of the HPMC polymer phase at 25 °C shifted to 1056 cm^{-1} in cast films prepared at 80 °C, whereas that in the cast film prepared at 120 °C

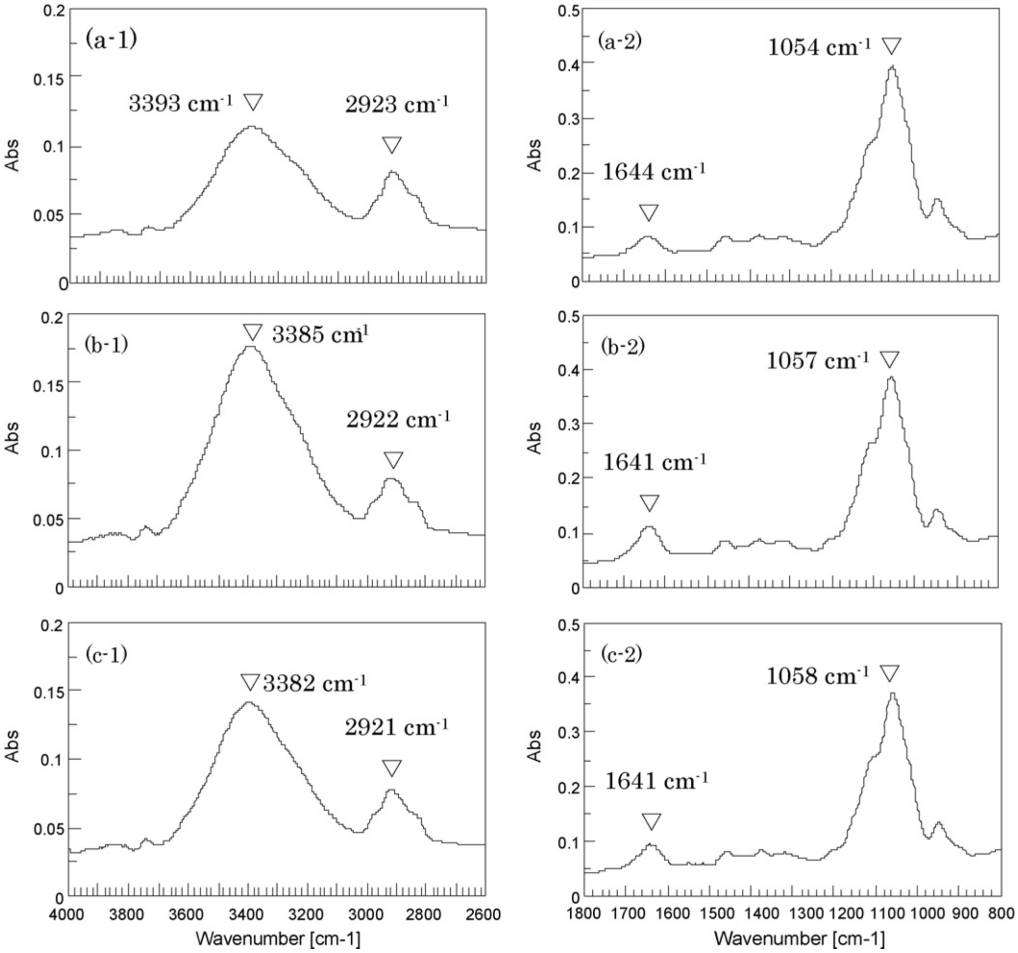

Fig. 11. FT-IR spectra of cast film consisting of HPMC and $CaCl_2$ blends prepared at 25 °C, 80 °C, and 120 °C. (a-1 and a-2): 25 °C, (b-1 and b-2): 80 °C and (c-1 and c-2): 120 °C.

did not shift. In contrast, the peak patterns in the 3400–4000 cm^{-1} and 1300–1700 cm^{-1} regions did not change when the preparation temperature was increased. As shown in Fig. 2, cast films consisting of HPMC/CLP blends formed the white films at 80 °C, whereas there was no white film formation in cast films prepared at 25 °C and 120 °C. Since the cast films prepared at 25 °C have profiles similar to those of the films prepared at 120 °C, the formation of the white film would be related to the molecular motion of the HPMC polymer phase.

Fig. 11 shows the ATR FT-IR spectra of cast films prepared at 25 °C, 80 °C, and 120 °C using solutions consisting of HPMC/$CaCl_2$ blends. The peak patterns at 1644 cm^{-1} and 3393 cm^{-1} corresponding to the adsorbed water and the hydrogen bonding in the polymer were both significantly affected by an increase in the preparation temperature of the cast films. In particular, the adsorption band at 1644 cm^{-1} corresponding to adsorbed water shifted to 1641 cm^{-1} in cast films prepared at 80 °C and at 120 °C. In general, the water in the film is known to be a plasticizer in various films. Therefore, the adsorption band at 3393 cm^{-1} corresponding to hydrogen bonding was also shifted significantly to 3385 cm^{-1} and 3382 cm^{-1} in cast films prepared at 80 °C and at 120 °C. Moreover, the peak at 2923 cm^{-1} corresponding to the CH_3 stretching shifted to 2922 cm^{-1} and 2921 cm^{-1} in cast films prepared at 80 °C and at 120 °C, respectively. In addition, the peak at 1054 cm^{-1} corresponding to the C–O–C and C–O stretching of the HPMC polymer phase stretching shifted to 1057 cm^{-1} and 1058 cm^{-1} in cast films prepared at 80 °C and at 120 °C. In contrast, the peak patterns at 1317 cm^{-1}, 1375 cm^{-1}, and 1455 cm^{-1} did not change when the preparation temperature was increased. As shown in Fig. 2, cast films consisting of HPMC/$CaCl_2$ blends formed the white films at 80 °C and at 120 °C, whereas no white film was formed in cast films prepared at 25 °C. These results suggest that the white films originating from HPMC/CLP and HPMC/$CaCl_2$ blends would be formed by the molecular behaviour related to the region associated with the C–O–C and C–O stretching and the CH_3 stretching of the HPMC polymer phase. In a previous study, we confirmed that the white film could be formed by the interaction with ionic Ca. In contrast, the water content of the white film consisting of HPMC/CLP blends was approximately 3.61–4.57%, whereas that of the films consisting of HPMC/$CaCl_2$ blends was approximately 13.16–15.68% (data not shown). Thus, the formation of the white films was not dependent on the water content in the case of the cast films comprising HPMC and calcium salts.

These results suggest that the formation of the white film may be caused by the change in the HPMC polymer phase brought about by an interaction with ionic Ca. Moreover, heating or drying may be required to ensure a strong interaction between HPMC and Ca ion.

4. Conclusions

A white film comprising HPMC and calcium salts was formed by the interaction between amorphous areas of HPMC and ionic Ca. From the results of the ATR FT-IR analyses, it was revealed that calcium salts affect the region associated with the C–O–C, C–O, and CH_3 stretching of the HPMC polymer phase. In a previous study, we reported that the white film could be applicable for pharmaceutical coating. In contrast, the white film was transformed into transparent films by the addition of purified water. In addition, the transformation time to transparent film from the white film was dependent on film thickness. These results suggest that the white film comprising HPMC and calcium salts could be applicable to time indicator.

References

Poter, S.C., 1989. Controlled-release film coating based on ethylcellulose. Drug Dev. Ind. Pharm. 15, 1495–1521.

O' Donnell, P.B., McGinity, J.W., 2000. Mechanical properties of polymeric films prepared from aqueous polymeric dipersions. In: McGinity, J.W. (Ed.), Aqueous Polymeric Coating for Pharmaceutical Dosage Forms, 2nd ed. Marcel Dekker Inc., New York, pp. 517–548.

Okhamafe, A.O., Iwebor, H.U., 1986. Proceedings of the 4th International Conference on Pharmaceutical Technology, vol. V, Paris, pp. 103–110.

Okhamafe, A.O., York, P., 1988. Studies of interaction phenomena in aqueous-based film coating containing soluble additives using thermal analysis techniques. J. Pharm. Sci. 77, 438–443.

Okhamafe, A.O., York, P., 1989. Thermal characterization of drug/polymer and excipient/polymer interations in some film coating formulation. J. Pharm. Pharmacol. 41, 1–6.

Sakata, Y., Shiraishi, S., Otsuka, M., 2006. A novel white film for pharmaceutical coating formed by interaction of calcium lactate pentahydrate with hydroxypropyl methylcellulose. Int. J. Pharm. 317, 120–126.

Bolhuis, G.K., Eissens, A.C., Zoestbergen, E., 2001. DC calcium lactate, a new filler–binder for direct compaction of tablets. Int. J. Pharm. 221, 77–86.

Hattori, M., Koga, T., Shimaya, Y., Saito, M., 1998a. Aqueous calcium thiocyanate solutions as a cellulose solvent structure and interactions with cellulose. Polym. J. 30, 43–48.

Hattori, M., Shimaya, Y., Saito, M., 1998b. Structural changes in wood pulp treated by 55 wt% aqueous calcium thiocyanate solution. Polym. J. 30, 37–42.

Hattori, M., Shimaya, Y., Saito, M., 1998c. Solubility and dissolved cellulose in aqueous calcium- and sodium-thiocyanate solution. Polym. J. 30, 49–55.

Bechard, S.R., Quraishi, O., Kwong, E., 1992. Film coating: effect of titanium dioxide concentration and film thickness on the photostability of nifedipine. Int. J. Pharm. 87, 133–139.

Kakinoki, K., Yamane, K., Teraoka, R., Otsuka, M., Matsuda, Y., 2004. Effect of relative humidity on the photocatalytic activity of titanium dioxide and photostability of famotidine. J. Pharm. Sci. 93, 582–589.

Chan, L.W., Wong, T.W., Chua, P.C., York, P., Heng, P.W.S., 2003. Anti-tack action of polyvinyl pyrrolidone on hydroxypropylmethylcellulose solution. Chem. Pharm. Bull. 51, 107–112.

Nyamweya, N., Hong, S.W., 2000. Assessment of polymer–polymer interactions in blends of HPMC and film forming polymers by modulated temperature differential scanning calorimetry. Pharm. Res. 17, 625–631.