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A novel white film for pharmaceutical coating formed by interaction of calcium lactate pentahydrate with hydroxypropyl methylcellulose

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Abstract

We have found that a white film forms on tablets when a coating solution consisting of hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG 6000) and calcium lactate pentahydrate (CLP) is used. The white film has also been found in casting film consisting of HPMC and CLP, and the surface state of coated tablets has been shown to be strongly affected by addition of PEG 6000. The aim of the present study was to investigate the mechanism of formation of this white film in order to derive an appropriate film prescription. Interaction among the base ingredients of the film was investigated using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform-infrared (FT-IR) spectroscopy. The casting film formed with HPMC and a large excess of PEG 6000 was found to be crystalline in form. In contrast, the amorphous film consisting of HPMC, PEG 6000 and excess CLP exhibited the crystallinity film by an excess addition of CLP. Although the crystalline film had many cracks, the amorphous film appeared to be excellent as a tablet coating. The most probable interaction sites between HPMC and CLP were demonstrated by FT-IR analysis of casting films consisting of HPMC, CLP and PVP.
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Keywords: HPMC; Calcium lactate pentahydrate; PEG 6000; Coating; White film

1. Introduction

Cellulosic and acrylic polymers used primarily for pharmaceutical coating both have good film-forming properties that enable the production of a tough coat, protecting against photolytic degradation and moisture, preventing changes in tablet shape, and masking the bitter taste of the tablet formulation (Poter, 1989; O'Donnell and McGinity, in press). Recently, cellulose has been attracting attention because of its natural reproducibility and high biodegradability. Moreover, hydroxypropyl methylcellulose (HPMC) is universally applicable as a pharmaceutical coating because it is a non-ionic and highly soluble polymer. Most of the additives incorporated in protective film are usually plasticizers, pigments, or other film-forming polymers. Titanium dioxide (TiO_2) is a pigment often included in the outer film as an agent that protects against photolytic degradation (Bechard et al., 1992) and masks the tablet surface. TiO_2 affects the physical properties of the film, such as strength and flexibility, and the disintegration behavior of the coated tablet. Makino et al. (1994) reported that the tablet surface blackens during coating with a white film when a large amount of TiO_2 is incorporated. On the other hand, 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 due to certain kinds of free radicals. Kakinoki et al. (2004) reported that famotidine was stable against irradiation without TiO_2, whereas it showed marked discoloration in the presence of TiO_2. This discoloration was significantly dependent on both the irradiation wavelength and the crystal form of TiO_2 at high humidity. Thus, white film containing TiO_2 is associated with various problems. Okhamafe and Iwebor (1986) have reported that the highly water-soluble additives citric acid and urea affect the moisture permeability of films based on HPMC and polyvinyl alcohol (PVA). Okhamafe and York (1988, 1989) have also reported that small amounts of ephedrine hydrochloride have a plasticizing effect in both HPMC and PVA films. The nature and degree of excipient/polymer interactions exert a significant influence on film properties. Calcium lactate

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pentahydrate (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 direct compaction of tablets, and Hattori et al. (1998a,b,c) have reported that aqueous $Ca(SCN)_2$ solution capable of dissolving cellulose might form a stable complex-like structure with it. Thus, calcium plays an important role in the functionality of cellulose films. However, no studies on the function of CLP in coating films have been reported. Recently, we found that coating solutions consisting of HPMC and CLP formed a white film after drying. Therefore the present study was conducted to evaluate the interaction between HPMC and PEG 6000, HPMC and CLP, and the mechanism of formation of white films.

2. Materials and methods

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. The structures of HPMC and CLP are shown in Fig. 1. Polyethylene glycol (PEG 6000) was purchased from Nakarai Chemicals Ltd., Japan.

2.2. Preparation of HPMC solutions

Coating solutions were prepared by weighing the desired amounts of HPMC, CLP and PEG 6000, mixing them with distilled water, and leaving the solutions to stand overnight. The concentrations of HPMC, CLP and PEG 6000 were kept constant at 5–8% (w/w), 1–6% (w/w) and 1–4% (w/w), respectively.

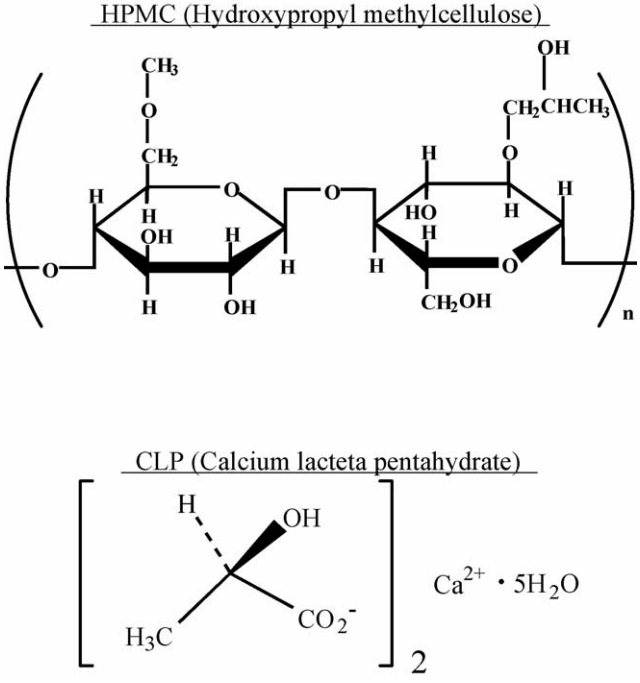

Fig. 1. Chemical structure of HPMC and CLP.

2.3. Preparation of cast films, sprayed films and coated tablets

Cast films were prepared by casting the solutions onto a clean glass plate and leaving them overnight at 50 °C to allow the solvent to evaporate. The sprayed films were prepared by spraying the coating solutions onto an immobilized Teflon sheet in a coating machine (Doria-coater type DRC-200) and allowing the solvent to evaporate at 70 °C. The cast and sprayed films were then peeled off and used for different tests (DSC, PXRD, FT-IR and SEM analysis). Film-coating of tablets was also performed with the same type of coating machine using the same coating solutions. The operating conditions for sprayed films and coating of tablets were: spray solution feed, 2 ml/min; spray air pressure, 1.5 kg/cm^2; blower rate, 45 l/min; blower temperature, 70 °C; rotation rate, 25 rpm.

2.4. Differential scanning calorimetry (DSC) analysis

Thermal analysis of the samples was performed with a DSC (DSC EXSTRA 6000 with a DSC 30E measuring cell; Seiko). Approximately 5 mg of 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 and 140 °C, using a nitrogen gas purge at 50 ml/min. Samples were prepared for measurements (DSC, PXRD and FT-IR analysis) by peeling off the cast and sprayed films, and grinding them to a fine powder (particle size less than 710 μm) in an agate mortar and pestle.

2.5. Powder X-ray diffraction (PXRD) analysis

PXRD 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: $2\theta = 5$–$60°$. The loosely packed sample was prepared by pouring the powder into the holder without compressing.

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

FT-IR spectra were obtained only for samples with HPMC-CLP ratios (% w/w) of 8:0, 8:1, 8:2, 8:3, 8:4, 8:6. A dispersion (about 1%) of the sample in potassium bromide (KBr) was prepared by mixing the mass with KBr. FT-IR spectra of the prepared mixture with KBr were obtained on a Nicolet Magna-IR 760 spectrometer in the 4000–400 cm^{-1} region. The number of scans was 400 and the resolution was 4 cm^{-1}.

2.7. Scanning electro microscopy (SEM) analysis

Samples were mounted onto aluminum stubs and gold coated in a sputter coater to a thickness of 10 μm. The coated samples

were then viewed at 400× magnification in the FE-SEM (JEOL, Tokyo, Japan). The beam accelerator voltage was set to 25 kV and the current was set to 12 μA.

3. Results

3.1. Casting films consisting of HPMC and CLP

Fig. 2 shows photographs of the casting films prepared using aqueous solutions of HPMC/PEG 6000 (8:1% (w/w)), HPMC/CLP (8:3% (w/w)) and HPMC/PEG 6000/CLP (8:1:3% (w/w)). All of these solutions were clear. After these solutions had been dried at 50 °C, the HPMC/PEG 6000 mixture was shown to form a clear cast film. On the other hand, the HPMC/CLP and HPMC/PEG 6000/CLP mixtures formed a white film. Unlike the cast film prepared from the suspension, the surface of these films did not show any white particles. The cast film prepared using HPMC/PEG 6000/CLP showed a tendency to be stronger than the film prepared using HPMC/CLP. Moreover, a white film was also formed from the solution consisting of HPMC and calcium chloride (not shown). These results suggested that the interaction between HPMC and CLP might be responsible for formation of the white film.

3.2. Interaction of HPMC and PEG 6000

A plasticizer is usually added as a component to improve the mechanical and conditional quality of the coating film. Honary and Orafai (2002) reported that the mechanical and thermo mechanical properties of cast films were affected by the molecular weight and concentration of the plasticizer, polyethylene glycol. Fig. 3A and B shows the DSC profiles of the HPMC, PEG 6000 and cast films obtained by the spray-drying method using a solution consisting of HPMC and PEG 6000. The DSC profiles of HPMC and PEG 6000 each showed a broad endothermic peak at 35–105 °C and an endothermic peak at 61.2 °C due to melting (Fig. 3A). In contrast, when HPMC and PEG 6000 were used in cast films at 8 and 1–4% (w/w), respectively, the endothermic peak was observed at 57.6 and 57.1 °C for films prepared using

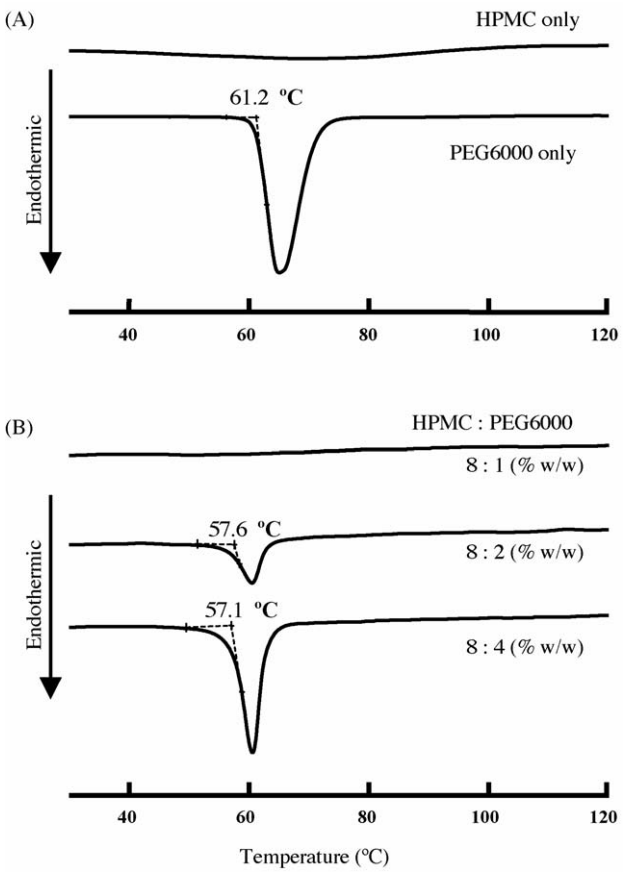

Fig. 3. DSC thermograph of HPMC, PEG 6000 and sprayed film consisting of HPMC and PEG 6000 blends.

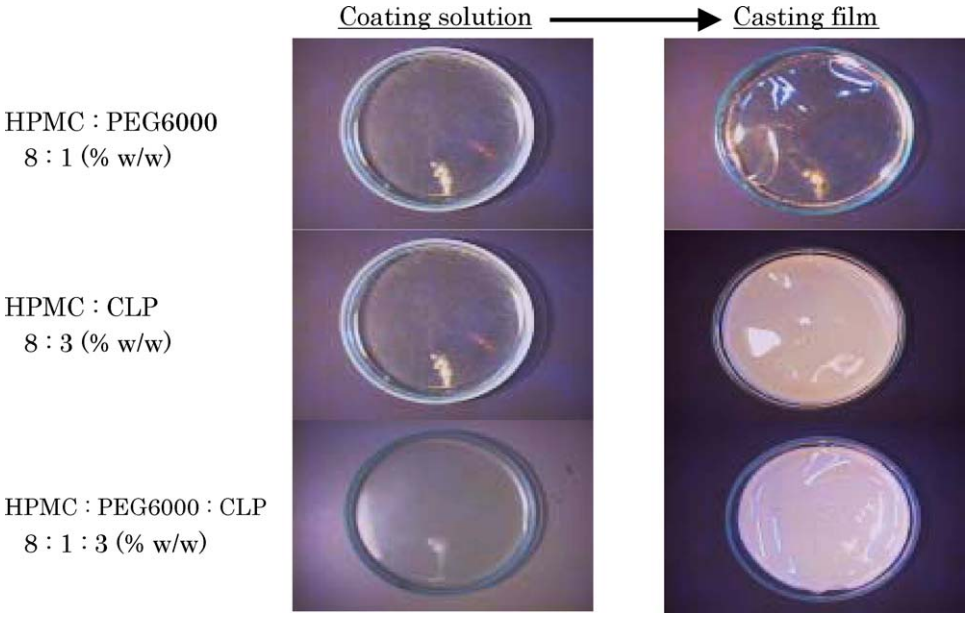

Fig. 2. Photograph of cast film consisting of HPMC and PEG 6000, HPMC and CLP, HPMC, PEG 6000 and CLP blends.

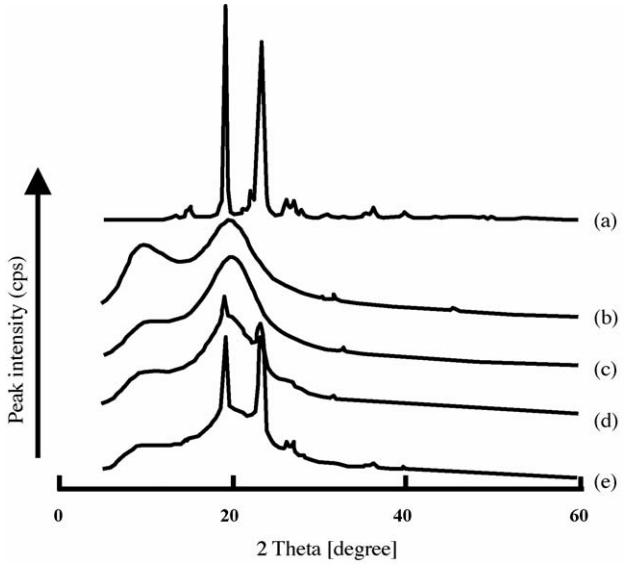

Fig. 4. PXRD patterns of sprayed film consisting of HPMC and PEG 6000 blends. Key: HPMC:PEG 6000, (a) PEG 6000, (b) HPMC, (c) 8:1% (w/w), (d) 8:2% (w/w), and (e) 8:4% (w/w).

a solution containing PEG 6000 at 2 and 4% (w/w), whereas this peak was not shown for a solution containing 1% (w/w) PEG 6000 (Fig. 3B). The observed area of the endothermic peak increased with increasing concentration of PEG 6000.

Fig. 4 shows the PXRD patterns of cast films consisting of HPMC/PEG 6000, HPMC only and PEG 6000 powder. The film prepared with HPMC and PEG 6000 powder showed two broad peaks (amorphous) and a crystalline diffraction pattern, respectively. The PXRD pattern of the cast film prepared with a blend of HPMC/PEG 6000 (8:1% (w/w)) showed two broad peaks similar to that for the cast film prepared using HPMC alone. However, the diffraction intensity of the first peak of the sprayed HPMC film decreased with increasing PEG 6000. Moreover, the PXRD profiles of the cast films of HPMC/PEG 6000 (8:2% (w/w)) and HPMC/PEG 6000 (8:4% (w/w)) showed crystalline diffraction peaks originating from PEG 6000. The plasticizer plays an important role in the strength of a polymer film, but when present in excess, it can reduce the film strength. Therefore, these results suggest that the HPMC/PEG 6000 ratio may play a very important role in the strength and physicochemical properties of HPMC film. Fig. 5 shows the SEMs of cast films consisting of HPMC and PEG 6000 blends. Many grooves were observed on the surface of films made with HPMC/PEG 6000 blends of 8:2 and 8:4% (w/w), although they were only slightly evident on film consisting of a blend of 8:1% (w/w).

Upon addition of excess PEG 6000, crystallization of PEG 6000 may proceed in the sprayed film during drying, as shown in Figs. 3 and 4. On the other hand, hardly any crystallization of PEG 6000 was observed on film consisting of HPMC/PEG 6000 at 8:1% (w/w).

These results suggest that film prepared using a HPMC/PEG 6000 ratio of 8:1% (w/w) may exhibit the most useful as a plasticizer of PEG 6000.

3.3. Interaction between HPMC and CLP

Fig. 6A shows the DSC profiles of sprayed films consisting of several blend ratios of HPMC and PEG 6000. The DSC profile of the film consisting of HPMC/PEG 6000 at 5:1% (w/w) indicated endothermic peaks at 56–57 °C. These endothermic peaks arising from the melting of PEG 6000 were not observed with an increasing ratio of HPMC. Fig. 6B shows the DSC profiles of sprayed films consisting of HPMC/PEG 6000/CLP blends. Sprayed films were prepared from coating solution containing HPMC ranging in concentration from 5 to 8, 1% (w/w) PEG 6000, and 3% (w/w) CLP respectively. The DSC profiles of sprayed film, obtained using coating solutions containing HPMC between 5 and 6% (w/w), each indicated endothermic peaks at 52.2 and 52.9 °C, although no endothermic peak was evident between 7 and 8% (w/w) HPMC.

Crystallization of PEG 6000 was observed upon addition of CLP to the HPMC/PEG 6000 6:1% (w/w) film, although PEG 6000 did not crystallize in film consisting of HPMC/PEG 6000 6:1% (w/w), as shown in Fig. 6A. This CLP may inhibit the interaction of HPMC and PEG 6000 in the process of formation of polymer film. Moreover, these results suggest that the degree of interaction between HPMC and CLP may be stronger than that between HPMC and PEG 6000.

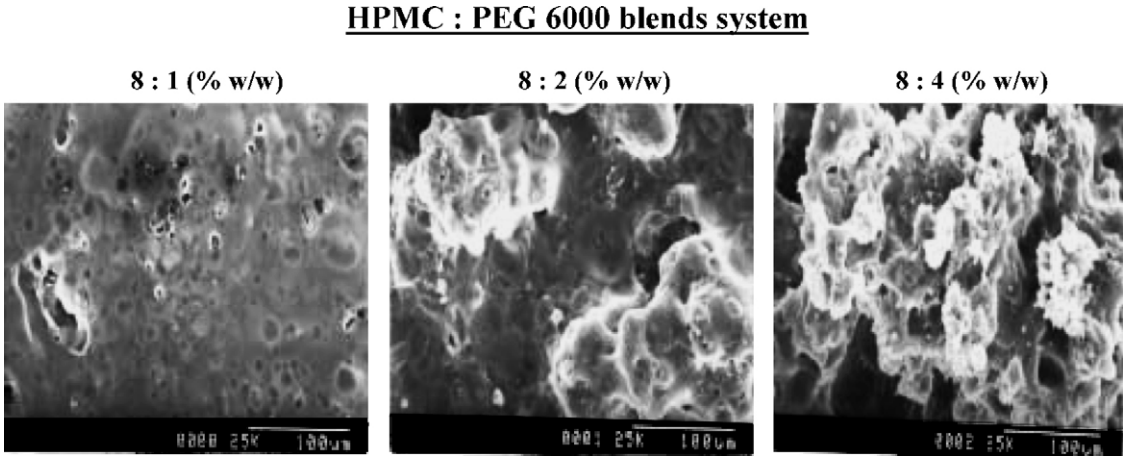

Fig. 5. SEMs of sprayed film consisting of HPMC and PEG 6000 blends.

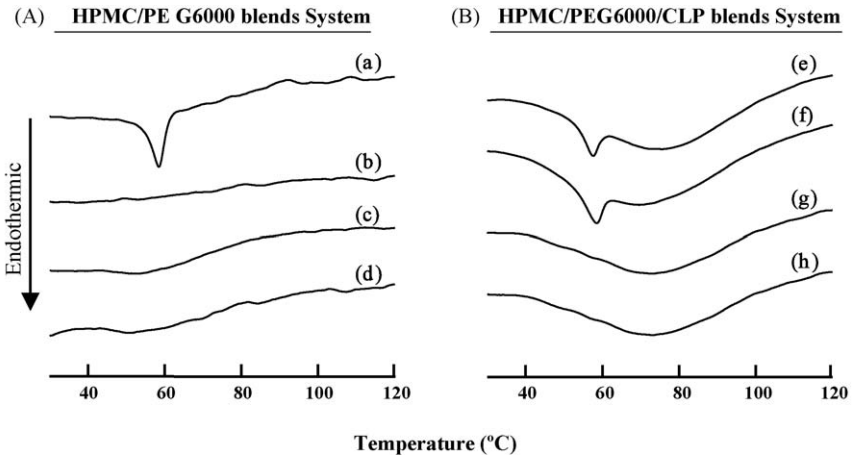

Fig. 6. DSC thermograph of sprayed film consisting of HPMC:PEG 6000 and HPMC:PEG 6000:CLP blends. Key: HPMC:PEG 6000 system, (a) 5:1% (w/w), (b) 6:1% (w/w), (c) 7:1% (w/w), (d) 8:1% (w/w), HPMC:PEG 6000:CLP system, (e) 5:1:3% (w/w), (f) 6:1:3% (w/w), (g) 7:1:3% (w/w), and (h) 8:1:3% (w/w).

Subsequently, the appearance of coated tablets prepared using the different coating solutions was compared. Fig. 7A and B shows photographs of coated tablets consisting of HPMC/PEG 6000/CLP blends. The surface state of coated tablets was affected significantly by the concentration ratio of HPMC/PEG 6000/CLP blends, as evidenced by the appearance of cracks at a concentration ratio of 6:1:3% (w/w) (Fig. 7A). On the other hand, no cracks were observed at a concentration ratio of 7:1:3% (w/w) (Fig. 7B). At a concentration ratio of 6:1:3% (w/w) for the HPMC/PEG 6000/CLP blend, the DSC profiles indicated an endothermic peak at 52.2 °C, but no such peak was evident at a concentration of 7:1:3% (w/w).

The appearance of coated tablets reflected the physicochemical properties of the cast film, and suggested that the ratio of HPMC, plasticizer (PEG 6000) and CLP might play a important role in the HPMC-coating process.

3.4. Interaction between HPMC and calcium gluconate (CG), and magnesium chloride (MC)

To confirm that formation of the white film was restricted by the interaction of CLP and HPMC, cast film was prepared using another calcium salt, calcium gluconate (CG), and a divalent metal salt, magnesium chloride (MC), instead of CLP.

The coating solution consisting of HPMC/PEG 6000 blends containing CG formed the white film in the same way as the HPMC/PEG 6000/CLP blends, but the coating solution containing MC did not (data not shown).

Fig. 8 shows the PXRD patterns of films consisting of HPMC/PEG 6000/CLP, HPMC/PEG 6000/CG and HPMC/PEG 6000/MC blends. The PXRD profiles of film consisting of HPMC/PEG 6000/CG blends indicated two broad diffraction patterns, as was the case for HPMC/PEG 6000/CLP blends. However, the diffraction intensity of HPMC/PEG 6000/CG blends was smaller than that of HPMC/PEG 6000/CLP blends. On the other hand, the PXRD profile of film consisting of HPMC/PEG 6000/MC blends showed a hallo pattern, and the structure of the films was almost amorphous. No crystalline peak was observed for each film. Thus, formation of white film may be attributable to interaction between cellulose and calcium ions. Moreover, from these results, it suggested that the divalent metal ion might interact with cellulose, although the interaction sites are probably different from those of ionic calcium and magnesium.

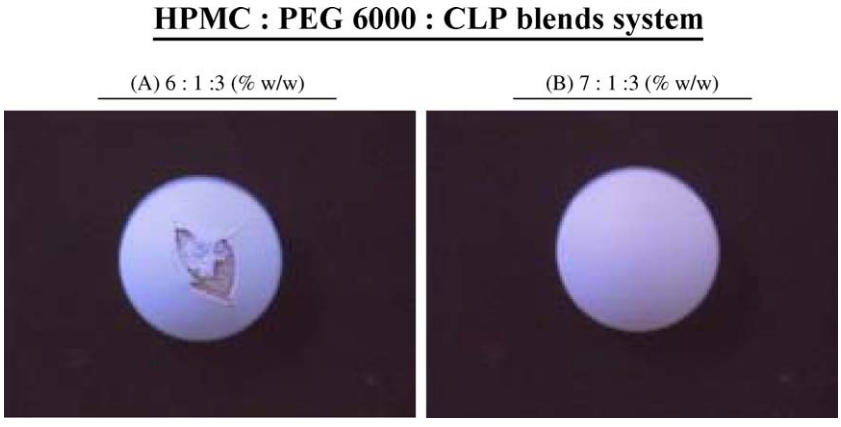

Fig. 7. Surface states of coated tablets consisting of HPMC, PEG 6000 and CLP blends.

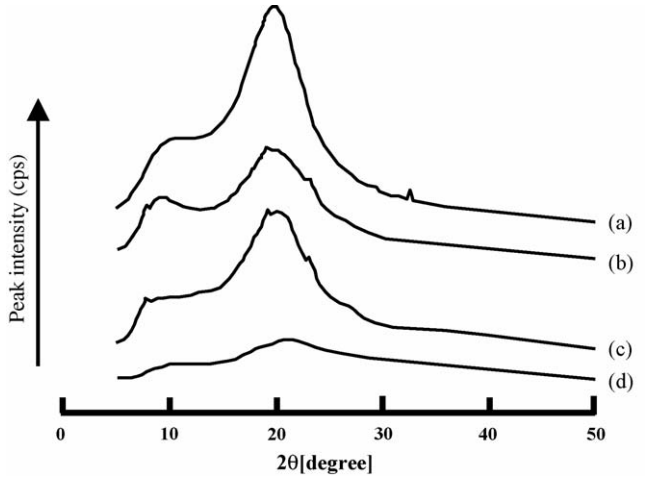

Fig. 8. PXRD patterns of sprayed film consisting of HPMC, PEG 6000, calcium gluconate, and magnesium chloride blends. Key: (a) HPMC/PEG 6000 (8:1% (w/w)), (b) HPMC/PEG 6000/CL (8:1:2% (w/w)), (c) HPMC/PEG 6000/CG (8:1:2% (w/w)), and (d) HPMC/PEG 6000/$MgCl_2$ (8:1:2% (w/w)).

To examine the interaction with cellulose and calcium in the film, HPMC-films with different CLP contents were prepared by the spray method. These PXRD patterns are shown in Fig. 9.

The shapes of the peaks arising from CLP were not evident in the diffraction profiles, and all films showed the broad two-peak amorphous pattern. Moreover, the peak intensities of HPMC films decreased with an increasing ratio of CLP.

Hattori et al. (1998a,b,c) reported that structural changes in cellulose occurred during the concentration of aqueous calcium thiocyanate ($Ca(SCN)_2$) solution, as confirmed by DSC and PXRD analysis. The PXRD patterns of cellulose in wood pulp indicate broad two peaks and an amorphous peak pattern, as is the case for HPMC. The structural change in cellulose upon interaction with ionic calcium may be involved in formation of the white color during drying of the coating solution.

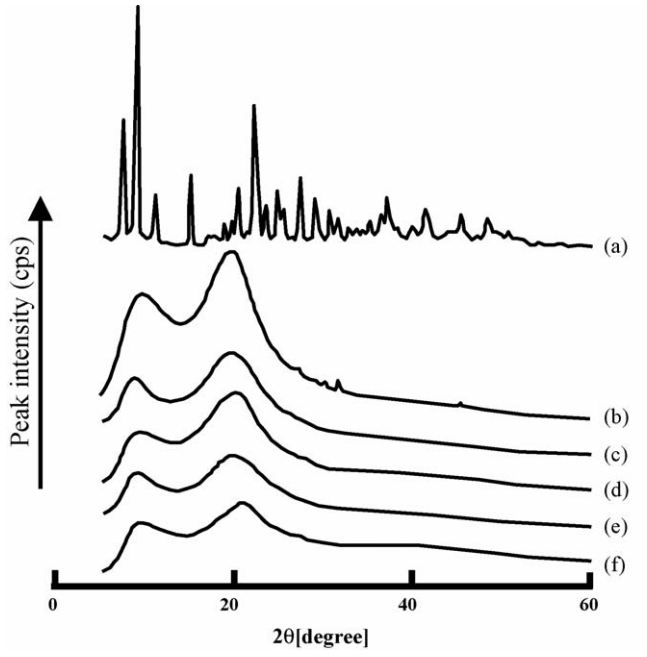

Fig. 9. PXRD patterns of sprayed film consisting of HPMC/CLP blends. Key: HPMC/CLP system, (a) CLP, (b) 8:1% (w/w), (c) 8:2% (w/w), (d) 8:3% (w/w), (e) 8:4% (w/w), (f) 8:6% (w/w).

3.5. Sites of interaction between HPMC and CLP

FT-IR spectroscopy 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 biological and synthetic apatites and related calcium phosphates (Legeros, 1991).

Fig. 10 shows the FT-IR spectra of films obtained using various ratios of blended HPMC/CLP. The functional groups associated with the HPMC polymer were CH, CH_2, CH_3, C–O–C, C–O, and H–O–H. The CH, CH_2 and CH_3 stretching absorption bands were found in the 1250–1460 and 2850–2980 cm^{-1} region. The C–O–C and C–O stretching alcohol absorption bands occurred at 1000 cm^{-1}. The absorption band at 1648 cm^{-1} corresponded to absorbed water (H–O–H). The broad absorption band in the 3500 cm^{-1} region represented hydrogen bonding in the polymer.

The peak patterns in the 1250–1460 and 2850–2980 cm^{-1} region associated with –CH, CH_2 and CH_3 stretching of the HPMC polymer phase were significantly different with an increase CLP. Their stretching region shifted to a lower field with increased CLP concentration with in the range 1–6% (w/w). The peak patterns of the films differed significantly with an increase in the concentration of CLP. The peak patterns in the 1000 cm^{-1} region associated with C–O–C and C–O stretching of the HPMC polymer phase also differed with the addition of CLP. Moreover, the peak patterns in the 1648 and 3500 cm^{-1} region corresponding to absorbed water and hydrogen bonding in the polymer were both significantly affected by addition of CLP. In particular, the adsorption band at 1648 cm^{-1} corresponding to adsorbed water shifted to a lower field upon addition of CLP. Usually, the water in the film is known to be a plasticizer in various films. Therefore, the adsorption band at 3500 cm^{-1} corresponding to

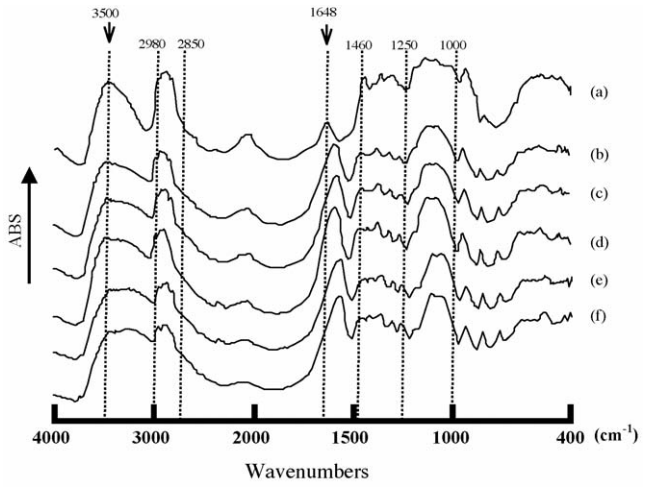

Fig. 10. FT-IR spectra of sprayed film consisting of HPMC and CLP blends. Key: HPMC/CLP system, (a) HPMC, (b) 8:1% (w/w), (c) 8:2% (w/w), (d) 8:3% (w/w), (e) 8:4% (w/w), and (f) 8:6% (w/w).

hydrogen bonding is also shifted significantly to a lower field. In contrast, film consisting of HPMC/CLP/PVP blends was not white. These results suggest that the sites of interaction between HPMC and CLP might be in a similar region between HPMC and PVP. These results obtained by FT-IR and PXRD suggest, therefore, that the white film might form through interaction of atoms in HPMC and ionic Ca.

4. Discussion

We studied the formation of white film prepared from coating solutions consisting of HPMC, PEG 6000 and CLP by the casting method, and also observed the appearance of coated tablets prepared using a coating machine. Moreover, the formation of white film was observed not only for HPMC/PEG 6000/CLP blends but also for HPMC/PEG 6000/CG blends. On the other hand, film consisting of HPMC/PEG 6000/MC blends did not show a white color either for casting film or for, coated tablets. Dorozhkin (2000) reported that there was no chemical interaction between HPMC and calcium phosphate. On the other hand, and Nguyen and Dupraz (1996) reported that multiphasic composite materials were formed by the mixture of biphasic calcium phosphate and HPMC. Moreover, Hattori et al. (1998a,b,c) reported that aqueous Ca $(SCN)_2$ solution, capable of dissolving cellulose, might form a stable complex-like structure with cellulose. These results suggested that the white film formed by interaction between HPMC and ionic Ca. However, the ratio of base ingredients consisting of HPMC, PEG 6000 and CLP blends significantly affects the appearance of coated tablets, due to breaking of the film at the top and edges of the tablet. The HPMC film (amorphous) was transformed into a crystalline film by adding excess PEG 6000. Consequently, the surface of the crystalline film showed higher distortion than amorphous film. Moreover, amorphous film consisting of HPMC and PEG 6000 was transformed into crystalline film by adding excess CLP, because the DSC profiles and PXRD patterns indicated a melting point corresponding to that of PEG 6000. Since interaction between HPMC and CLP appears to be stronger than that between HPMC and PEG 6000, the results suggested that PEG 6000 and CLP interact at the same or similar sites of the HPMC phase. The white film was obtained by compounding of HPMC/CLP and HPMC/CG blends, but casting films consisting of these blends did not form the white film upon addition of PVP (data not shown). Nyamweya and Hong (2000) reported that HPMC and PVP were miscible, as evidenced by a single glass transition temperature. 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 aqueous HPMC solution. The PVP molecule only contains 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 a basic carbonyl group of PVP. Therefore, the present results suggest that Ca and PVP interact with the same or similar site of HPMC. Moreover, Hattori et al. (1998a,b,c) have reported that Ca $(NCS)_2$ and cellulose might form a stable complex-like structure. It has also been postulated that the most likely structure of Ca $(NCS)_2$ and cellulose is formed by coordination of two oxygen atoms (O (5) and O (6)) in glucopyranose unit to Ca atoms. Therefore, the white film formed from HPMC and CLP blends might arise at the same or a similar site of action between Ca $(NCS)_2$ and cellulose.

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