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Effects of sugar ester and hydroxypropyl methylcellulose on the physicochemical stability of amorphous cefditoren pivoxil in aqueous suspension

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Abstract

The improvement in physicochemical stability of amorphous cefditoren pivoxil (CDTR-PI) in aqueous suspensions by addition of sugar ester (SE) and hydroxypropyl methylcellulose (HPMC) was explained by prolonging the induction period prior to crystallization and the reduction in crystal peak intensity. Furthermore, the stabilizing effect of these additives in a multiple additive system was greater than in a single additive system. To determine the mechanism, by which these additives stabilized the amorphous CDTR-PI, we evaluated the surface states of CDTR-PI in suspension by measuring Raman spectra and zeta potential. The change in Raman spectra demonstrated that SE and HPMC interacted with CDTR-PI at the same interaction sites on CDTR-PI. The zeta potential reflected the adsorption phenomena of the additives and indicated that both SE and HPMC adsorbed onto particles of CDTR-PI with no apparent competitive interaction and the response was complementary. It was considered, based on this study, that HPMC and SE would stabilize amorphous CDTR-PI by different mechanisms; HPMC would mainly inhibit crystal growth by small amount of adsorption and SE would inhibit both crystal growth and nucleation by large amount of adsorption. This was considered to result in the hybrid effect in the multiple additive system.

Keywords: Cefditoren pivoxil; Raman spectrum; Zeta potential; Physicochemical stability; Amorphous; Suspension

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1. Introduction

Pharmaceutical suspensions are commonly used as a dosage form for drug administration, particularly to children who cannot ingest solid oral dosage forms

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such as tablets and capsules. Also, suspensions of nanoparticles have been recently used to improve the bioavailability of a drug.

Physicochemical stability is an important requirement for pharmaceutical suspensions. Previously, reports regarding the physicochemical stability of suspensions have been published (Duro et al., 1998a, 1998b; Verger et al., 1998). These reports described the stability of suspensions from viewpoints of redispersibility and aggregation prevention. We considered two viewpoints in assessing the physicochemical stability of suspensions; the dispersing states of suspensions described previously and the crystallinity of a drug substance. Physicochemical stability viewed from a crystallographic perspective has sparse reporting in the literature. The evaluations of surface states and molecular interactions are considered to be important when evaluating stability from this viewpoint, because there is a high probability that crystallinity is affected by contact with dispersion medium and/or additives.

A number of reports using zeta potential analysis to evaluate the surface property of substances dispersed in suspensions have been published (Duro et al., 1998a, 1998b; Takeuchi et al., 1998; Verger et al., 1998; Pettersson et al., 2000; Terayama et al., 2001; Bouhamed et al., 2003; Tartakovsky et al., 2003). High potential values contribute to the stabilization effect of dispersing states with a repulsive force. Duro et al. (1998a, 1998b) used zeta potential analysis to demonstrate the relationship between adsorption of additives to drug particles and the stability (redispersibility) of suspensions. Furthermore, Pettersson et al. (2000) indicated that the zeta potential was related to the adsorption of a polymer to alumina particles. Adsorption states, such as the co-adsorption phenomena and the configuration of a polymer adsorbing to particles, were studied by measuring the zeta potential (Terayama et al., 2001; Bouhamed et al., 2003).

Spectroscopic techniques such as Raman and IR are used as tools for the evaluation of molecular interaction. Demonstrations of hydrogen-bond interaction using IR or Raman have been reported frequently in the literature (Touitou et al., 1994; Gao and Singh, 1997; Broman et al., 2001; Savolainen et al., 2003; Sajan et al., 2004). Since water interferes with IR detecting a change of dipole moment, the measurement of an aqueous suspension using IR is impossible. But, Raman detects polarization changes and water tends to have minimal interference with measurements. Therefore, Raman has an advantage when measuring an aqueous suspension.

The purpose of this study is to evaluate the effects of additives on the stability of amorphous drug in aqueous suspension from a crystallographic viewpoint, and to clarify the mechanism by which additives affect stability using zeta potential analysis and Raman spectroscopy.

2. Materials and methods

2.1. Samples

Amorphous CDTR-PI was prepared by Meiji Seika Kaisha Ltd. Sugar ester (DK Ester SS: SE) was obtained from Dai-Ichi Kogyo Seiyaku Co. Ltd. (Japan) and hydroxypropyl methylcellulose 2910 (TC-5R: HPMC) was purchased from Shin-Etsu Chemical Co. Ltd. (Japan).

2.2. Preparation of suspension

We prepared aqueous solutions of additives by dissolving SE and TC-5R into water at each concentration used for 0–1%. We added the solution to amorphous CDTR-PI slowly while stirring, and CDTR-PI was dispersed to a concentration of 13 mg/ml.

2.3. Physicochemical stability of amorphous drug in suspension

We stored the suspensions at 25 °C and evaluated the physicochemical stability using a RINT-2200-Model Powder X-ray Diffraction (XRD) instrument manufactured by Rigaku Co. (Japan). The samples were centrifuged at 3000 rpm for 5 min; supernatants were discarded and the residue was dried under reduced pressure (at room temperature with silica gel) for 18 h. The resulting powders were measured using XRD at a scan range of 9–13°, a scan speed of 0.5 °/min, a voltage of 40 kV, and a current of 40 mA. When the ratio of signal to noise at 10.8° was less than 3, we accepted the sample as amorphous.

2.4. Raman spectroscopy

We measured Raman spectra of the suspensions using a STR-250-Model Laser Raman Spectrometer with a microscope made by Seki Technotron Co. (Japan). A laser at a wavelength of 514.5 nm and power of 40 mW was used. The resolution for measurement was 1 cm^{-1}. This instrument uses the Grams analysis software, and we separated the obtained peaks using this software with Gaussian theory. The ratios of peak intensity to the peak near 1500 cm^{-1} were estimated.

2.5. Zeta potential

We measured electrophoretic mobilities of the suspensions using a Zetasizer 3000HS_A manufactured by Malvern Instruments Ltd. (UK). The zeta potential was calculated based on electrophoretic mobility by means of the Smoluchowski approximation shown in Eq. (1):

$$U_E = \frac{\varepsilon\zeta}{\eta} \tag{1}$$

where U_E is the electrophoretic mobility, ζ is the zeta potential, ε is the dielectric constant, and η is the viscosity.

2.6. Particle size

Volume mean diameter of dispersed CDTR-PI in each suspension was evaluated by laser diffraction method using a Microtrac 9320-X100 manufactured by Microtrac Inc. (US).

2.7. Adsorption amount and drug solubility

Additives amount in the supernatant of suspension, before and after dispersing, was determined as follows. We calculated the adsorption amount from the depletion amount of additives before and after dispersing. Each suspension was centrifuged at 3000 rpm for 15 min, the supernatant was filtered through a 0.45 μm pore-diameter membrane. The HPMC amount in the filtrate was determined by gas chromatography (The Japanese Pharmacopeia XIII, 1996). The SE in the filtrate was colored by Anthrone method (Ministry of Health and Welfare, 1982), the UV absorbance at 620 nm was measured. Since HPMC was also colored by Anthrone method, we calculated SE amount in SE/HPMC system by subtracting the UV absorbance resulting from HPMC estimated by gas chromatography.

We determined CDTR-PI solubility in each suspension by measuring the UV absorbance at 230 nm of the filtrate.

2.8. Redispersibility

Thirty millilitres of suspension were sealed in a 50 ml glass tube of diameter 35 mm and stored at 25 °C for 6 h. Redispersibility, the time needed to completely redisperse the sediment forming during storage, was determined by rotating the laid tube at 50 rpm.

3. Results and discussion

3.1. Physicochemical stability of amorphous drug in aqueous suspension

Fig. 1 shows the powder X-ray diffraction (XRD) pattern of CDTR-PI stored at 25 °C in water, as an example. Crystal polymorphism has not been observed for CDTR-PI, and the diffraction peak at 10.8° is one of the characteristic peaks of a CDTR-PI crystal. We used this peak intensity to evaluate the physicochemical stability of the samples because the peak first appears when the samples crystallize. When the ratio of signal to noise is less than 3, the signal is considered below detection limit. Therefore, when the ratio of signal to noise at 10.8° was less than 3, we accepted the sample as amorphous.

Table 1 shows the physicochemical stability of amorphous CDTR-PI in various suspensions. Figs. 2–4 show the change in the XRD peak intensity for CDTR-PI stored at 25 °C in various suspensions. When no additive was used, CDTR-PI in water (polar solvent) crystallized in 2 days. To clarify the crystallization mechanism of CDTR-PI, we also evaluated the

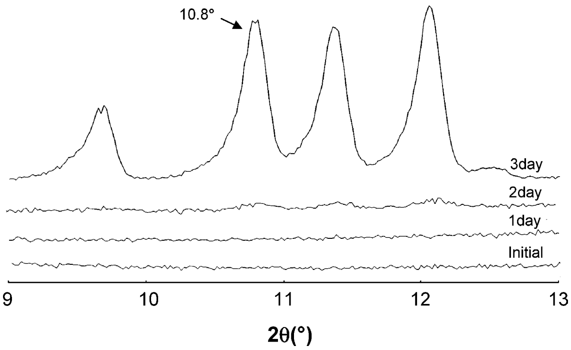

Fig. 1. Powder X-ray diffraction (XRD) pattern of CDTR-PI stored at 25 °C in water.

Table 1
Physicochemical stability of amorphous CDTR-PI in aqueous suspension stored at 25 °C

Additives (%)		Storage time (day)								Induction period (day)
SE	HPMC	Initial	1	2	3	5	7	10	14	
0	0	A	A	C	C	C	C	C	C	1
0.001	0	A	A	A	C	C	C	C	C	2
0.05	0	A	A	A	A	C	C	C	C	3
1	0	A	A	A	A	A	C	C	C	5
0	0.01	A	A	A	C	C	C	C	C	2
0	0.5	A	A	A	A	C	C	C	C	3
0	1	A	A	A	A	C	C	C	C	3
0.05	0.01	A	A	A	A	C	C	C	C	3
0.05	0.5	A	A	A	A	A	A	A	C	10
0.05	1	A	A	A	A	A	A	A	A	>14

A: amorphous, C: crystal.

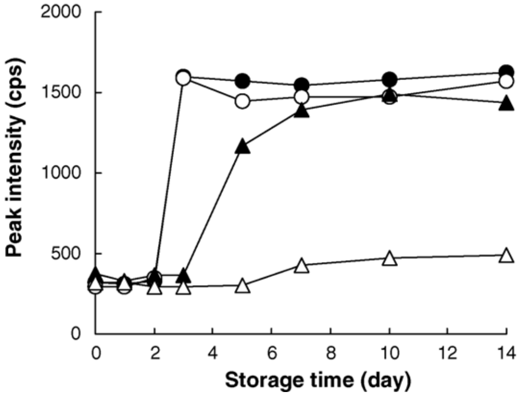

Fig. 2. Change in XRD peak intensities of CDTR-PI stored at 25 °C in a SE suspension system (●) without additive, (○) 0.001% SE, (▲) 0.05% SE, and (△) 1% SE.

physicochemical stability of amorphous CDTR-PI in *n*-hexane (non-polar solvent). CDTR-PI in *n*-hexane did not crystallize for 2 weeks (not shown in data). From the results, it was suggested that CDTR-PI crystallized from the surface by contact with a polar solvent. The possibility that a polar solvent affected the polar groups of CDTR-PI on the surface was considered, and this suggested that the polar groups of CDTR-PI had some relation to crystallization.

When either SE or HPMC was added, the induction period for CDTR-PI crystallization was prolonged and XRD peak intensity was decreased (Table 1, Figs. 2 and 3). This suggested that SE and HPMC stabilized amorphous CDTR-PI in water; SE and HPMC would inhibit crystal nucleation and growth. This stabi-

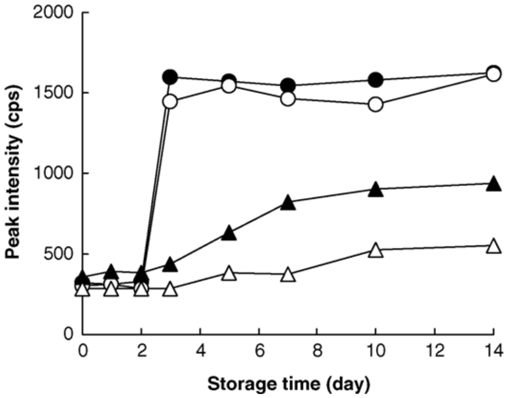

Fig. 3. Change in XRD peak intensities of CDTR-PI stored at 25 °C in an HPMC suspension system (●) without additive, (○) 0.01% HPMC, (▲) 0.5% HPMC, and (△) 1% SE.

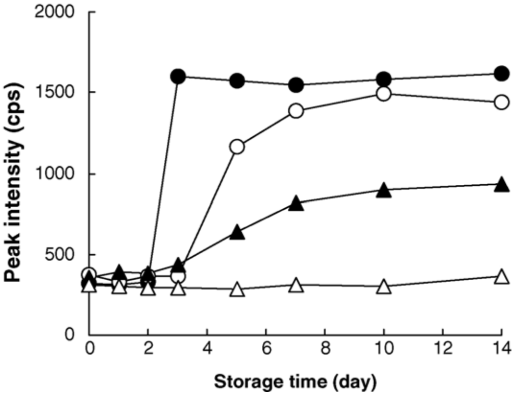

Fig. 4. Hybrid effect of SE and HPMC on physicochemical stability of CDTR-PI in suspensions stored at 25 °C (●) without additive, (○) 0.05% SE, (▲) 0.5% SE, (△) 0.05% SE and 0.5% HPMC.

lizing effect increased in relation to an increase in either SE or HPMC concentration. SE showed a greater contribution to prolonging the induction period compared to the HPMC.

There was a 3-day induction period when 0.05 SE or 0.5% HPMC was added. On the other hand, an induction period of 10 days was seen upon addition of a mixture of the additives (0.05 and 0.5% HPMC) demonstrating a much longer induction period compared to suspensions that added a single additive (Table 1). The XRD peak intensity in the mixed additives suspensions was also decreased compared with those in the single additive suspension (Fig. 4). These results clarified that the physicochemical stability of amorphous CDTR-PI in water in the multiple additives system (SE and HPMC) was improved compared with that in the single additive system.

Consequently, it was suggested that CDTR-PI in water crystallized from the surface, and that additives would affect the physicochemical stability of amorphous CDTR-PI by contact on the surface of CDTR-PI.

3.2. *Evaluation of interaction between drug and additive by Raman spectrometry*

The surface states of CDTR-PI in various suspensions using Raman spectrometry were evaluated as a means to clarify the effect of additives on the physicochemical stability of amorphous CDTR-PI in suspension. Since the Raman spectrum of water is essentially a single broad, weak band at 3500 cm^{-1}, water tends to have minimal interference with the vibrational modes from most drugs. Since the Raman spectrum is observed as the scattering from solid samples in aqueous suspensions (Bugay and Williams, 1995; Williams et al., 2004), its results are considered a partial reflection of the surface states of a drug in aqueous suspension. Moreover, the Raman scattering peaks in this study were observed in the measurements focusing on the solid part of a suspension, and the measurements focusing on the solution part of a suspension detected no peak (not shown in data).

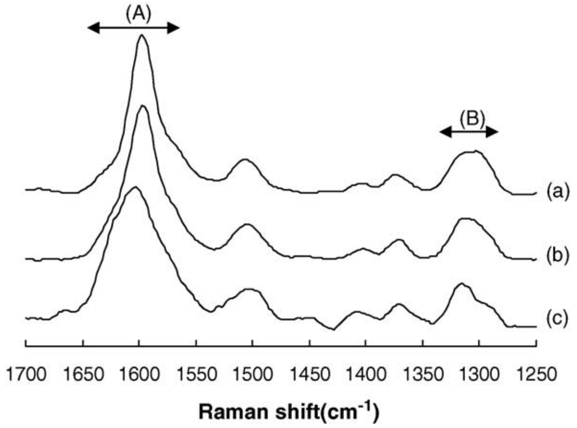

Fig. 5. Raman spectra of CDTR-PI in various suspensions: (a) suspended CDTR-PI in water, (b) suspended CDTR-PI in 1% HPMC, and (c) suspended CDTR-PI in 1% SE, (A) conjugated diene and (B) ester.

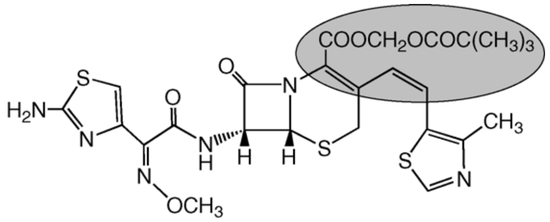

Fig. 6. Chemical structure of CDTR-PI.

Raman spectra of CDTR-PI in various suspensions and the chemical structure of CDTR-PI are shown in Figs. 5 and 6. When either 1% SE or 1% HPMC was added, the peak shapes at 1600 cm^{-1} (A) and 1300 cm^{-1} (B) changed compared with Raman spectrum of suspension without the additive. Peak (A) and (B) resulted from a conjugated diene and ester, respectively (Okuyama et al., 1989). To progressively evaluate the peaks, we separated them using Gaussian theory as shown in Fig. 7. The peaks at 1600 and 1300 cm^{-1}

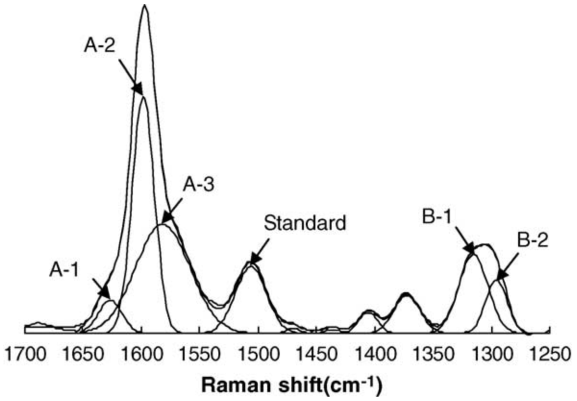

Fig. 7. Peak separation in Raman of suspended CDTR-PI in water.

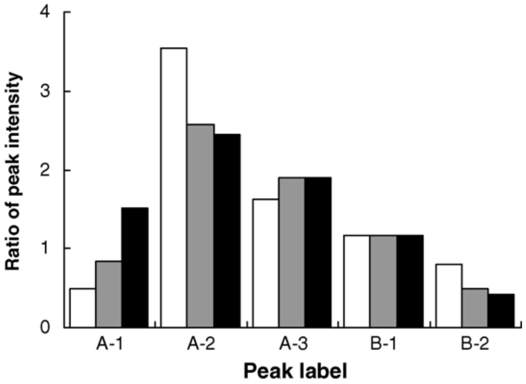

Fig. 8. Ratios of peak intensities vs. standard peak of 1500 cm^{-1} in Raman spectra of CDTR-PI in various suspensions (☐) suspended CDTR-PI in water, (▩) suspended CDTR-PI in 1% HPMC, and (■) suspended CDTR-PI in 1% SE.

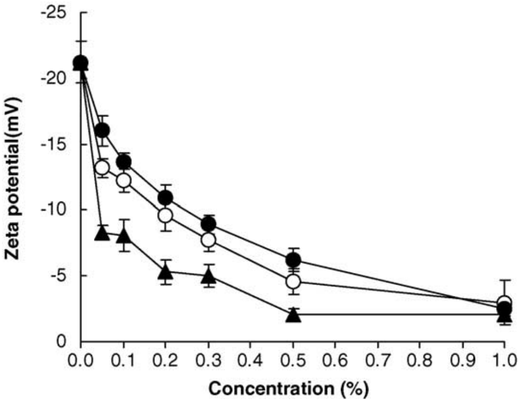

Fig. 9. Zeta potential of CDTR-PI in suspension (●) single additive system (HPMC), (○) single additive system (SE), and (▲) multiple additive system (SE and HPMC).

were separated into three sub-peaks (A-1, A-2, and A-3) and two sub-peaks (B-1 and B-2), respectively. Furthermore, we compared the ratios of peak intensities as to these peaks (A-1–B-2) using the peak intensity at 1500 cm^{-1} as a standard. Since the peak shape at 1500 cm^{-1} did not change upon addition of additives it was used as a standard. The ratios of peak intensity in Raman spectra of various suspensions are shown in Fig. 8. In the peaks resulting from a conjugated diene near 1600 cm^{-1} (due to the addition of additives) the ratios of peak intensity decreased in peak (A-2) and increased in peak (A-1). In the peaks resulting from an ester near 1300 cm^{-1}, the ratios of peak intensity decreased in peak (B-2) upon the addition of additives. The change in peak shape was supported by peak separation. These results suggested that the addition of additives caused the blue shift of a conjugated diene and the change of molecular states of an ester. The usefulness of spectroscopic techniques, such as IR and Raman, to investigate molecular interaction has been reported previously. For example, Touitou et al. (1994) has reported that iodine caused a shift of the N–H stretching band of the polyurethane polymer to a lower frequency in IR spectra due to the formation of a complex with intramolecular hydrogen bonding. Thus, the molecular states, such as the hydrogen-bond interaction, are measurable by using these spectroscopic techniques. Since the tendency for change in Raman spectra was similar between the SE and HPMC systems, the additive interaction site of CDTR-PI was considered the same. It was considered that CDTR-PI and the additives had some interaction at the location surrounded by the conjugated diene and ester (Fig. 6). Furthermore, the change of peak shapes in Raman spectrum of CDTR-PI in 1% SE was greater compared with that in 1% HPMC suggesting the interaction of CDTR-PI with SE was greater than that with HPMC.

3.3. Evaluation of adsorption phenomena of additive onto drug by zeta potential

It was reported that the adsorption of HPMC on the drug particles affected the magnitude of the zeta potential (Duro et al., 1998a). As a means to clarify the effect of additives on the physicochemical stability of amorphous CDTR-PI in suspensions, we evaluated the adsorption phenomena of additives on CDTR-PI by measuring the zeta potential of suspensions.

The values of zeta potential versus the concentration of additives are shown in Fig. 9. At an additive concentration of 0%, the zeta potential of CDTR-PI was −21 mV. CDTR-PI was considered to have a negative charge due to the presence of carbonyl groups. Upon addition of either SE or HPMC, the magnitude of the zeta potential decreased and approached zero in relation to increased additive concentration. From this result, it was considered that the adsorption of additives, which are non-ionic substances, to the particles of CDTR-PI would contribute to the change of zeta potential and that the additives would shield the charge of CDTR-PI by increasing the distance between the parti-

Table 2
Properties determined for aqueous suspension

	Additives (%) (SE/HPMC)			
	0/0	0.1/0	0/0.1	0.1/0.1
Particle size of CDTR-PI (μm)	7.0	7.6	6.6	7.7
Adsorption amount onto CDTR-PI particles (mg/g)				
SE	–	12.6	–	12.3
HPMC	–	–	2.0	2.1
Total	–	12.6	2.0	14.5
Redispersibility (s)	131	77	88	50
Drug solubility (μg/ml)	80.0	211.5	84.7	228.6

cles surface and the shear plane. The zeta potential for the SE system was closer to zero than that in the HPMC system. Here, properties of suspension are shown in Table 2. Particle size of CDTR-PI in suspension did not change by the addition of additives. The adsorption amount upon addition of 0.1% SE or 0.1% HPMC was 12.6 and 2.0 mg/g, respectively. The reduction of redispersing time and the increase of drug solubility in the SE system were greater than those in the HPMC system. These results suggested that the interaction of SE with CDTR-PI would be greater than that of HPMC. This was also supported by a change in peak shapes seen in the Raman spectra for the SE system being greater than that for the HPMC system (Figs. 5 and 8).

Furthermore, the magnitude of the zeta potential in the multiple additive system (the combined use of SE and HPMC) showed a remarkable decrease compared with the single system. Here, the total adsorption amount of SE and HPMC in the multiple additive system (0.1% SE and 0.1% HPMC) was increased to 14.5 mg/g (SE: 12.3 mg/g, HPMC: 2.1 mg/g, Table 2). The redipersibility and drug solubility indicated the behaviour according to the adsorption phenomena. These results suggested that SE and HPMC adsorbed onto the CDTR-PI particles non-competitively. However, the interaction sites of CDTR-PI to SE and HPMC would be the same as seen in the Raman result. So, it was considered that SE and HPMC would adsorb onto the CDTR-PI particles with a non-competitive yet complementary interaction. Chemical structures of SE and HPMC are shown in Fig. 10. SE is monoester, and MW is ca. 600. HPMC consists of 160 glucose units, and MW is ca. 30,000. In considering the non-competitive adsorption, the free interaction sites would remain due to some structural hindrance of additives in adsorbing onto CDTR-PI particles, because SE and HPMC have long chain structures (alkyl or cellulose). That is, the additives would not always fill all interaction sites. Furthermore, HPMC is a large molecule compared with SE. Therefore, the degree of structural hindrance in HPMC would be greater than that in SE. It was considered that HPMC would adsorb onto the more limited interaction sites via structural hindrance compared with SE. On the other hand, it was considered that SE would adsorb onto the interaction sites, which HPMC could not adsorb due to its size. The structural hindrance would result in the non-competitive and complementary adsorption.

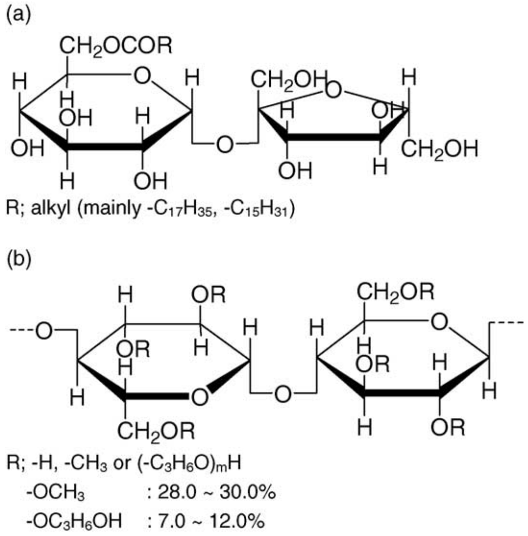

Fig. 10. Chemical structures of additives: (a) SE and (b) HPMC.

3.4. Relationship between physicochemical stability and adsorption

The result of the physicochemical stability of amorphous CDTR-PI in aqueous suspensions was consistent with the adsorption phenomena of additives to CDTR-PI particles, in that the improvement of stability and the increase of adsorption were observed in the multiple additive systems. Although the HPMC interacted with CDTR-PI, the extent was very small as shown in the Raman spectra and the adsorption phenomena. The HPMC contributed to the reduction of peak intensity in XRD rather than the prolongation of the induction period until crystallization. It was considered that HPMC would contribute primarily to the inhibition of crystal growth by some effect (viscous effect, physical shielding from polar solvent, etc.) resulting from small amount of adsorption. On the other hand, the interaction between SE and CDTR-PI was great and contributed to both the reduction of crystal peak intensity and the prolongation of induction period. Therefore, it was considered that SE would contribute to the inhibition of not only crystal growth but also crystal nucleation by some effect (electrostatic effect, etc.) resulting from the large amount of adsorption. The stabilizing mechanism was considered to be different between SE and HPMC and to be due to the difference of adsorption states. This could be the reason why the hybrid effect in physicochemical stability was observed in the multiple additive system.

4. Conclusion

The physicochemical stability of amorphous CDTR-PI in aqueous suspensions was improved by the addition of additives. Since it was considered that the physicochemical stability of amorphous CDTR-PI in aqueous suspensions was affected by the contact with additives on the surface, we evaluated the surface states of CDTR-PI in suspensions by measuring Raman spectra and zeta potential. It was clarified using Raman spectra that both SE and HPMC had affinity for the same interaction sites on CDTR-PI. Furthermore, the peak separation technique in Raman spectra demonstrated that SE interacted with CDTR-PI to a greater extent compared to HPMC. The measurement of zeta potential indicated that SE and HPMC had a non-competitive and complementary effect on the adsorption of CDTR-PI particles. From these results, it was considered that HPMC and SE would stabilize amorphous CDTR-PI by different mechanisms resulting from their different adsorption states; HPMC would inhibit mainly the crystal growth, and SE would inhibit both crystal growth and crystal nucleation.

Consequently, we could demonstrate a mechanism, whereby the additives stabilized amorphous CDTR-PI in aqueous suspensions, from the results of Raman and zeta potential. This study proposed that Raman spectroscopy and zeta potential were useful to investigate the physicochemical stability of amorphous drug in suspensions.

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