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Changes in surface properties by granulation and physicochemical stability of granulated amorphous cefditoren pivoxil with additives

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Abstract

The evaluation of the physicochemical stability of granules of amorphous cefditoren pivoxil (CDTR-PI), alone or with polymers, demonstrated that granulated amorphous CDTR-PI with hydroxypropyl methylcellulose was the most stable. We measured glass transition temperature by differential scanning calorimetry (DSC). The molecular mobility of the whole granules did not change, and it was not consistent with the results of the evaluation of physicochemical stability. Peak shifts were observed in IR spectra of amorphous CDTR-PI with polymers after granulation, and the shifts were similar to those observed for spray-dried samples. Furthermore, the shifts were not observed after the granules were ground. Acid–base parameters, which were also measured by inverse gas chromatography (IGC), changed after granulation. These results suggested that on the surface of the granules, CDTR-PI and the polymers would be mixed monomolecularly, as in the spray-dried samples. The changes in the molecular state of a drug when mixed monomolecularly with a polymer on the surface of granules were successfully confirmed by IGC and IR.

Keywords: Cefditoren pivoxil; Inverse gas chromatography; Surface energy; Physicochemical stability; Amorphous; Enthalpy relaxation

1. Introduction

Generally, the granules containing drug substances and additives are heterogeneous systems in which each component forms a particle by aggregation or adhesion. And they are roughly distinguished from homogeneous systems in which components are mixed monomolecularly such as a solid dispersion prepared by spray-drying. As to solid dispersion, which is considered as a homogeneous system, the examples of physicochemical stabilization of amorphous materials by the addition of polymers have been reported in large numbers. On the other hand, only a few examples of stabilization of heterogeneous systems, such as granules, have been reported.

In the evaluation of the physicochemical stability of solid dispersion, the measurement of relaxation times and glass transition temperatures has been reported

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(Hancock and Zografi, 1994; Hancock et al., 1995; Shamblin and Zografi, 1998; Matsumoto and Zografi, 1999; Royall et al., 1999; Tong and Zografi, 1999; Van den Mooter et al., 1999; Nyamweya and Hoag, 2000; Passerini and Craig, 2001; Christensen et al., 2002). The enthalpy of amorphous material is relaxed by isothermal aging. The time until it reaches certain extent of relaxation can be expressed as relaxation time. Relaxation time is a parameter that correlates with molecular mobility, and the evaluation of relaxation time using DSC has been reported in large numbers.

On the other hand, when we consider the influence of additives on drug substances during the granulation process, we can suppose that some changes occur on the contact interface. As to the evaluation of the surface of two components, there are several parameters, such as spectra, surface free energy, and surface glass transition temperature, that should be analyzed. In the cause of spectra, infrared (IR) absorption spectrometry and near-infrared (NIR) absorption spectrometry are commonly used in the research of pharmaceuticals. Comparing them, IR is lower in energy than NIR. Therefore, IR spectrometry is considered to measure the regions nearer to the surface than NIR spectrometry. Furthermore, among various methods of IR spectrometry, the diffuse reflection method is suited for the direct measurement of granules without destroying them. As to the measurement of surface free energy, contact angle and inverse gas chromatography (IGC) and so on are used. Concerning the contact angle method, there are two problems. First, it is difficult to choose solvents in which samples do not dissolve. Second, in case of measurement by dropping a solvent on the compressed surface, the results are easily affected by the compression procedure (Grimesey et al., 2002). IGC utilizes the adsorption of the probe molecule to samples. Since the adsorption phenomena occur on regions of high activity (high energy), it is considered that this method can be useful to measure specific regions of high energy, such as the surface. IGC is used to measure surface free energy and glass transition temperature in the area of polymers (Delarue and Giampaoli, 2000; Hamieh and Schultz, 2002; Segeren et al., 2002; Uhlmann and Schneider, 2002; Zafeiropoulos et al., 2002). Recently, it has come to be used in pharmaceutical research as well, and the measurement of surface free energy has been reported (Buckton et al., 1999; Newell et al., 2001; Grimesey et al., 2002).

The purposes of this research are to clarify the effects of the granulation process with additives on the physicochemical stability of drug substances, and to verify the usefulness of IGC as a means to evaluate the surface properties.

2. Materials and methods

2.1. Samples

CDTR-PI crystal was manufactured by Meiji Seika Kaisha, Ltd., and amorphous CDTR-PI was prepared by spray-drying. Hydroxypropylcellulose (HPC-L) was obtained from Nippon Soda Co., Ltd. (Japan) and hydroxypropyl methylcellulose 2910 (TC-5R) was purchased from Shin-Etsu Chemical Co., Ltd., (Japan) both of which conformed to the requirements of the Japanese Pharmacopoeia. Guaranteed reagents were used for various organic solvents. Potassium bromide was used to analyze IR spectra.

2.2. Preparation of granules

We granulated amorphous CDTR-PI alone or amorphous CDTR-PI with polymers (at the rate of 5:1) by adding water in an MP-01-Model Multiplex Granulator (Powrex Corporation, Japan).

2.3. Preparation of spray-dried samples

CDTR-PI alone or CDTR-PI with polymers (at the rate of 1:1 or 1:5) were prepared. They were dissolved in a mixture of dichloromethane and methanol (1:1), at a CDTR-PI concentration of 2.5%. These liquids were spray-dried at an inlet temperature of 100 °C and at a flow rate of 10 g/min using the GS-31-Model Spray Drier made by Yamato Scientific Co., Ltd. (Japan).

2.4. Evaluation of the physicochemical stability of granules

Various granules were stored at 25 °C and at a relative humidity (RH) of 81, 91 and 97% for a week to control their water content. After that, they were put in glass airtight bottles, and stored at 40 °C for

a week. Before and after storage at 40 °C, a sample of 0.2 g was suspended in 15 ml of water. They were centrifuged at 3000 rpm for 5 min, and after the supernatants was discarded, they were dried under reduced pressure (at room temperature, with silica gel) for 18 h. The obtained powders were measured using the RINT-2200-Model Powder X-ray Diffraction (XRD) equipment made by Rigaku Co. (Japan) 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.

2.5. Measurement of relaxation time

A sample of about 5 mg placed on an aluminum pan was measured under nitrogen gas flow using a DSC-7-Model DSC equipment made by Perkin-Elmer, Inc. (USA). This equipment loads Pyris as the analysis software; we used the DSC mode for aging, and modulated-temperature DSC (MTDSC) mode to detect glass transition temperatures and enthalpy recovery peaks. The procedures for the measurements were as follows. The samples were heated from 30 °C to the aging temperatures at the rate of 40 °C/min, held isothermally for a definite period of time, and subsequently cooled to 30 °C at 40 °C/min in DSC mode. Then, they were reheated to 180 °C at the rate of 20 °C/min in MTDSC mode. In MTDSC mode, the heating process and isothermal process were alternately repeated for 15 s each. The aging times were 0, 0.5, 1, 2, 4 and 8 h. Enthalpy values were calibrated with indium.

The maximum enthalpy recovery ΔH_∞ was calculated from Eq. (1):

$$\Delta H_\infty = \Delta C_p(T_g - T_a) \tag{1}$$

where T_a is the aging temperature (°C), T_g is the glass transition temperature (°C), and ΔC_p is the change in heat capacity (J/g °C). From the obtained maximum enthalpy recovery, the extent of relaxation at time t, $\Phi(t)$ was calculated using Eq. (2):

$$\Phi(t) = 1 - \frac{\Delta H}{\Delta H_\infty} \tag{2}$$

where ΔH is the enthalpy recovery. We applied the obtained extent of relaxation and aging times to Kohlrausch–Williams–Watts formula shown in Eq. (3) using the nonlinear least squares method:

$$\Phi(t) = \exp\left(-\left(\frac{t}{\tau}\right)^\beta\right) \tag{3}$$

where t is the aging time, τ is the mean relaxation time and β is the relaxation time distribution parameter ($0 < \beta < 1$) (Hancock et al., 1995). The initial parameters of the nonlinear least squares method were $\tau = 50$ and $\beta = 0.5$. Furthermore, Eq. (4) was applied when the extent of relaxation at aging time 0 was not 1.

$$\Phi(t) = \exp\left(-\left(\frac{t}{\tau}\right)^\beta\right) - (1 - \Phi(0)) \tag{4}$$

2.6. Water contents and glass transition temperatures

The samples were stored at 25 °C and at 20, 43, 61, 81 and 97% RH for a day. The procedure to measure water content was as follows. A sample of 0.2 g was dried at 60 °C for 3 h under reduced pressure. Then, water content was calculated as the loss on drying. As to glass transition temperature, samples of about 5 mg placed in closed pans for liquids were measured under nitrogen gas flow using DSC-7. They were heated from 30 °C to 180 °C at the rate of 20 °C/min in MTDSC mode, where the heating process and isothermal process were alternately repeated for 15 s each.

In another experiment, we measured glass transition temperatures of samples with a water content of 0%. Samples of about 5 mg placed in open pans were measured under nitrogen gas flow using DSC-7 according to the described method.

2.7. Measurement of diffuse reflection infrared (IR) absorption spectra

IR spectra of samples were measured by the diffuse reflection method at the resolution of 4 cm^{-1} using PARAGON 1000-Model Fourier Transform Infrared (FT-IR) Spectrometer made by Perkin Elmer, Inc.

2.8. Acid–base parameters

Samples of 100–300 mg were packed into silanized glass columns with 3 mm inside diameter and 30 cm in length, and measured by inverse gas chromatography (IGC, Surface Measurement Systems Ltd., UK). After equilibration at 303 K for 3 h, we measured acid–base parameters at a flow rate of 10 cm^3/min and a column temperature of 303 K using helium as the carrier gas.

For probes, *n*-heptane, *n*-octane, *n*-nonane, *n*-decane, ethyl acetate, chloroform and acetone were used.

The adsorption free energy of a probe molecule $-\Delta G_0$ is given by Eq. (7):

$$-\Delta G_0 = RT \ln V_N + C \quad (7)$$

where R is the gas constant, V_N is the net retention volume, and C is a constant. Furthermore, $-\Delta G_0$ is related to the work of adhesion W_A by Eq. (8):

$$-\Delta G_0 = N_A a W_A \quad (8)$$

where N_A is Avogadro's number and a is the surface area of the adsorbed probe molecule. Here, the work of adhesion is shown by Eq. (9) as a geometric mean of the dispersive surface energy of solid and liquid:

$$W_A = 2(\gamma_S^D \gamma_L^D)^{1/2} \quad (9)$$

where γ_S^D and γ_L^D are the dispersive surface energy of the solid and probe, respectively. Eq. (10) is derived from Eqs. (7)–(9).

$$RT \ln V_N = 2N_A(\gamma_S^D)^{1/2} a(\gamma_L^D)^{1/2} - C \quad (10)$$

If $RT \ln V_N$ versus $a(\gamma_L^D)^{1/2}$ is plotted, a straight line can be obtained in alkanes. The vertical distance between the data points of a polar probe and the alkane line is the specific energy of adsorption $-\Delta G^{AB}$. Here, the values of a and γ_L^D were taken from the literature (Schultz et al., 1987; Nardin and Papirer, 1990). According to the acid–base theory of Gutmann, liquids are characterized as electron donors or base number (DN) and electron acceptors or acid number (AN), and AN is corrected to take into account dispersive contributions by Riddle and Fowkes to give AN*. $-\Delta G^{AB}$ is shown by Eq. (11) using an acid parameter K_A and a base parameter K_D (Newell et al., 2001; Grimesey et al., 2002).

$$-\Delta G^{AB} = K_A DN + K_D AN^* \quad (11)$$

By plotting $-\Delta G^{AB}/AN^*$ versus DN/AN^*, K_A and K_D were calculated. And K_D/K_A is used to describe the acidic or basic nature of solid materials.

3. Results and discussion

3.1. Physicochemical stability of granules

Fig. 1 shows the powder X-ray diffraction (XRD) pattern of CDTR-PI crystal. Crystal polymorphism has not been observed as to CDTR-PI, and the diffraction peak at 10.8° is one of the characteristic peaks of CDTR-PI crystal. We used this peak intensity to evaluate the physicochemical stability of samples, because the peak appeared firstly when the samples crystallized. Fig. 2 shows the representative XRD patterns of humidified granules before (a) and after (b) storage at 40 °C. Samples remained amorphous during humidification, because the crystallization rate of each sample would be slow sufficiently at 25 °C. And the peak intensity of the samples changed after storage at 40 °C. The relationship between water content and the XRD peak intensity is shown in Fig. 3. By storage at 40 °C for a week, the peak intensity of the granulated

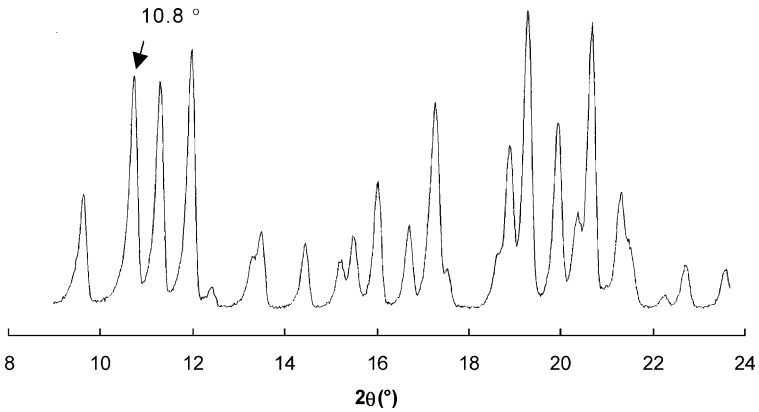

Fig. 1. Powder X-ray diffraction (XRD) pattern of CDTR-PI crystal.

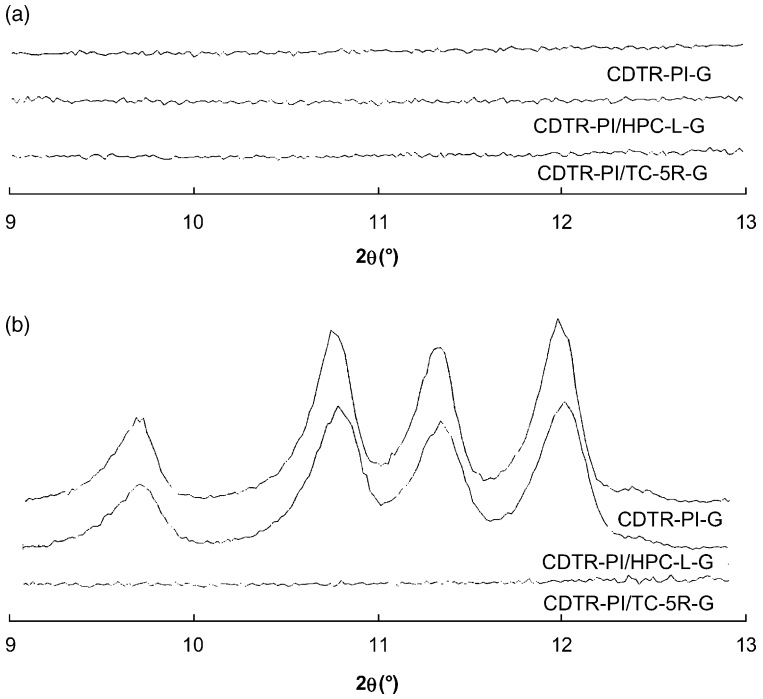

Fig. 2. XRD patterns of granulated CDTR-PI samples after humidification at 25 °C and 97% RH (a) Before storage at 40 °C for a week, (b) After storage at 40 °C for a week.

CDTR-PI alone and with HPC-L increased, resulting in the crystallization of the samples. On the other hand, the granulated CDTR-PI with TC-5R remained amorphous. This proved that the physicochemical stability of CDTR-PI in the wet state having a high water content was improved by granulation with TC-5R.

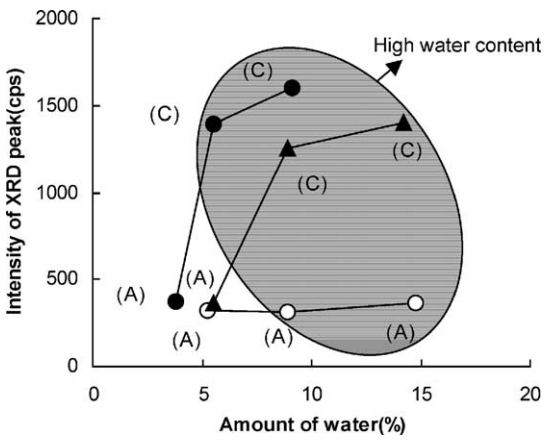

Fig. 3. Change in XRD peak intensity at 10.8° of granulated CDTR-PI samples after storage at 40 °C for a week. (●) Granulated CDTR-PI, ○, Granulated CDTR-PI with TC-5R (5:1), (▲) Granulated CDTR-PI with HPC-L (5:1), (A), Amorphous (C), Crystal.

3.2. Effects of polymers on the molecular mobility of samples

Effects of polymers on the molecular mobility of samples were studied. It was considered to be impossible to measure at one aging temperature without crystallization and within a proper measuring time, because the difference of molecular mobility among samples was great. Therefore, we used two aging temperatures (50 and 80 °C) on this study.

Table 1 shows the relaxation times of various spray-dried samples. At the aging temperature of 80 °C, the relaxation time of the spray-dried CDTR-PI with TC-5R (CDTR-PI/TC-5R) was slightly extended in comparison with that of the spray-dried CDTR-PI alone (CDTR-PI). At the aging temperature of 50 °C, the relaxation time of the spray-dried CDTR-PI with HPC-L (CDTR-PI/HPC-L) was remarkably reduced in comparison with the spray-dried CDTR-PI alone

Table 1
Relaxation times of spray-dried CDTR-PI alone and with polymer

Aging temperature (°C)	Sample	τ (h)	β
80	CDTR-PI	44	0.66
	CDTR-PI /TC-5R (1:1)	89	0.61
50	CDTR-PI	6202	0.57
	CDTR-PI /HPC-L (1:1)	51	0.56

β, the relaxation time distribution parameter.

(CDTR-PI). These results proved that the molecular mobility of CDTR-PI was affected by the addition of polymers; it was slightly lower with TC-5R and higher with HPC-L on a dry condition.

3.3. Relationship between molecular mobility and physical stability of samples

Figs. 4 and 5 show the glass transition temperature of various spray-dried samples and granules in relation to the amount of water. The glass transition temperatures of spray-dried samples with polymer were individually different. Compared with the spray-dried CDTR-PI alone, the glass transition temperature of spray-dried CDTR-PI with HPC-L was lower when the water content was low, and that of spray-dried CDTR-PI with TC-5R was higher when the water content was high.

The relaxation time and glass transition temperature obtained suggested that the molecular mobility of

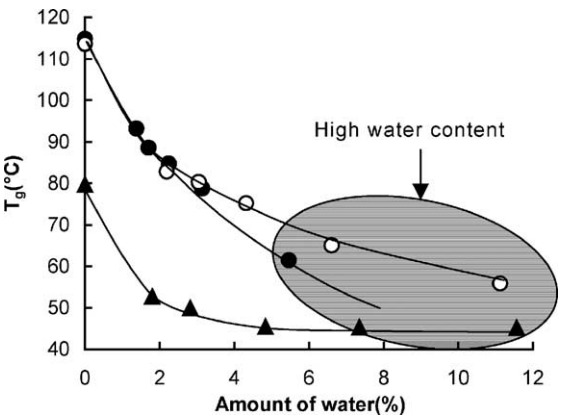

Fig. 4. Glass transition temperatures of spray-dried CDTR-PI samples containing different amounts of water (●) Spray-dried CDTR-PI, (○) Spray-dried CDTR-PI with TC-5R (1:1), (▲) Spray-dried CDTR-PI with HPC-L (1:1).

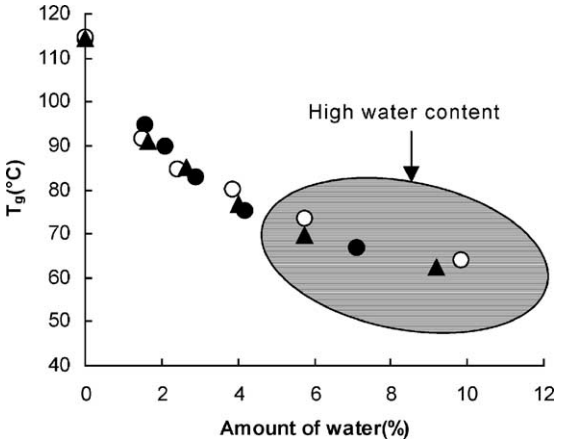

Fig. 5. Glass transition temperature of granulated CDTR-PI samples containing different amounts of waters. (●) Granulated CDTR-PI, (○) Granulated CDTR-PI with TC-5R (5:1), (▲) Granulated CDTR-PI with HPC-L (5:1).

spray-dried CDTR-PI changed when polymers were added (solid dispersion).

As to granules, there was no difference among samples in glass transition temperature regardless of the content of water (Fig. 5), and this finding was not consistent with physicochemical stability (Fig. 3). As a possible explanation, we could consider the following. The drug and additives interacted on the surface where both contacted each other. Since DSC detected the heat changes of the whole samples, it could not detect the heat changes of the specific regions, such as the surface, during the measurement of glass transition temperature. Assuming that the drug and additives were in a state similar to that of spray-dried samples (solid dispersion) on the surface of granules, the results of the evaluation of physicochemical stability were reasonable. In other words, the physicochemical stability of granules in a wet state (high water content) showed a tendency similar to that of the glass transition temperature (molecular mobility) of spray-dried samples with a high water content. To verify this assumption, we evaluated the surface of the samples.

3.4. Spectroscopic analysis of the sample surface by diffuse reflection infrared absorption spectrometry

Tables 2 and 3 show the diffuse reflection infrared (IR) spectra of various samples. As to the granulated or spray-dried amorphous CDTR-PI alone, there was

Table 2
Diffuse reflection infrared absorption (IR) spectra of physical mixtures and granules of CDTR-PI alone and with polymer

		Drug:Polymer	Wavenumber (cm^{-1})		
			1	2	3
CDTR-PI	Intact	–	1787	1752	1679
	Granule	–	1786	1752	1680
CDTR-PI/TC-5R	Physical mixture	5:1	1787	1752	1679
	Granule	5:1	*1790*	*1754*	*1687*
	Ground		1787	1752	1681
CDTR-PI/HPC-L	Physical mixture	5:1	1787	1752	1680
	Granule	5:1	*1784*	*1754*	*1687*
	Ground		1787	1752	1680

1, C=O stretching vibration (β-lactam), 2, C=O stretching vibration (ester), 3, C=O stretching vibration (amide).

Table 3
Diffuse reflection infrared absorption (IR) spectra of physical mixtures and spray-dried samples of CDTR-PI alone and with polymer

		Drug:Polymer	Wavenumber (cm^{-1})		
			1	2	3
CDTR-PI	Intact	–	1787	1752	1679
	Spray-dried	–	1787	1752	1679
CDTR-PI/TC-5R	Physical mixture	1:1	1787	1752	1679
	Spray-dried	1:1	*1791*	*1754*	*1682*
		1:5	*1792*	*1754*	*1683*
CDTR-PI/HPC-L	Physical mixture	1:1	1787	1752	1679
	Spray-dried	1:1	*1790*	*1754*	1680
		1:5	*1791*	*1754*	1680

1, C=O stretching vibration (β-lactam), 2, C=O stretching vibration (ester), 3, C=O stretching vibration (amide).

no change in the peaks before and after granulation or spray-drying. And the peaks of physical mixtures with polymers were consistent with those of intact CDTR-PI. On the other hand, we detected peak shifts on the granulated or spray-dried CDTR-PI with polymers in carbonyl stretching vibrations of β-lactam, ester, and amide, compared with the physical mixture. Furthermore, when the granules were ground, the peak shifts were not observed any more. As an example, Fig. 6 shows IR shifts of CDTR-PI samples with TC-5R compared with physical mixture. The IR shift of granules in carbonyl stretching vibration of β-lactam was 2.8 cm^{-1}, and the shift decreased to 0.1 cm^{-1} after the granules were ground. This suggested that the granules with polymers were heterogeneous systems, and some change occurred only on the surface. Since the peak shifts in carbonyl groups of granules with polymers were similar to those in spray-dried samples, it was considered that the surface state of granules was similar to that of spray-dried samples (solid dispersion). Consequently, it was suggested that drug and polymers mixed monomolecularly on the surface of granules, and interacted with each other.

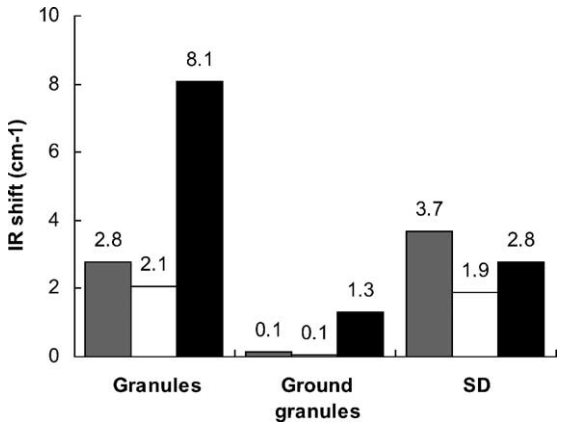

Fig. 6. IR shifts of CDTR-PI samples with TC-5R compared with physical mixture (■), C=O stretching vibration (β-lactam), (□) C=O stretching vibration (ester), (■) C=O stretching vibration (amide).

On the other hand, the glass transition temperature of each polymer would be different as reported (Nyamweya and Hoag, 2000). It was considered that the molecular mobility of polymer influenced that of the drug interacting with polymer, and resulted in the difference of glass transition temperatures shown in Fig. 4.

Although the amount ratio of surface to whole granules would be very small, the surface interaction affected the physicochemical stability enormously. Assuming that the crystallization would occur on the surface of granules firstly with the influence of adsorbed moisture, it was considered to be reasonable that the surface interaction contributed to the physicochemical stability of whole granules.

3.5. Acid–base parameters of the granules surface

Fig. 7 shows the surface acid–base parameters of samples before and after granulation. The values of K_D/K_A after granulation increased compared with before granulation. Furthermore, the increase of K_D/K_A on CDTR-PI with polymer after granulation was large compared with CDTR-PI alone. It was considered that the exposure of electron donating groups, such as carbonyl, resulted in an increase of K_D/K_A after granulation; the electron donating properties (K_D/K_A) increased according to the increase of ratio of the electron donating groups on the surface of granules. In the granulation process, phenomena as follows were expected to occur. Drug and polymers would dissolve in water and interact with each other, and the interaction site would be fixed on the surface of samples by drying. Thus, it was considered that the interaction site was exposed on the surface. The result of surface acid–base parameters was consistent with IR spectra in that the surface carbonyl groups changed.

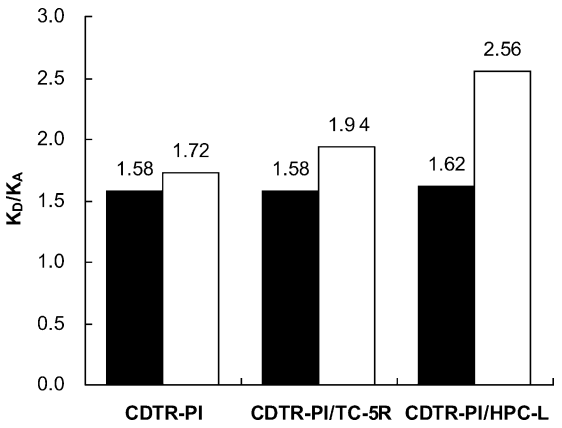

Fig. 7. Surface acid–base parameters of CDTR-PI samples before and after granulation measured by IGC at 0% RH: (■) before granulation; (□) after granulation.

4. Conclusion

The physicochemical stability of granulated CDTR-PI under wet conditions was improved by the addition of TC-5R. The molecular mobility of spray-dried samples changed by the addition of polymers. On the other hand, the molecular mobility of the whole granules did not change, and it was not consistent with the results of the evaluation of physicochemical stability. The results of diffuse reflection IR and IGC demonstrated that the surface state of granulated CDTR-PI with polymers was similar to that of spray-dried samples (solid dispersion). It was clarified by surface measurements (diffuse reflection IR and IGC) that the granules were heterogeneous systems, and drug and polymer interacted with each other only on the surface. Furthermore, the physicochemical stability of granules was consistent with the molecular mobility of spray-dried samples. Consequently, we could demonstrate the physicochemical stability of granules based on the property of the granules surface and the molecular mobility of spray-dried samples.

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