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A New Thermo-Sensitive Fatty Acid Complex. The Mechanism and Its Applicability to a Drug Delivery System

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A thermo-sensitive fatty acid-drug crystalline complex was prepared. The mechanism for the thermo-sensitivity was investigated by the powder X-ray diffractometry and the infrared spectroscopy, and its applicability to a thermo-responsive drug delivery system was discussed.

It is important to establish a drug delivery system (DDS) to ensure the high efficacy and minimal side effects of a medicine. The applicability of polymer gel has been studied for a thermo-sensitive DDS,[1] such as the properties of the polymer, swelling and contraction with changing temperature. However, there is still a difficult problem to unify the reticulation of the gel structure and the content of the drug in the gel. The discovery of a new thermo-sensitive compound has a high academic value. Fatty acids (FA) have polymorphs and their crystal structure changes at the transition temperature.[2] On the other hand, we have found that FAs form crystalline complexes with drugs with a constant molar ratio.[3] The FA-drug crystalline complexes should have a transition temperature and the crystal structure should change at the transition temperature as does FA alone. Therefore, we tried to apply the properties of the FA-drug crystalline complex to a thermo-sensitive DDS. This is a new concept which is quite different from the conventional method.[1] For the study on the thermo-sensitivity of the FA-drug complex, we used the FA-nicotinamide (NAA) crystalline complex, FA-NAA, as a model experiment. The stoichiometry and physicochemical properties of FA-NAA whose carbon number of FA is 14—18 have already been reported.[3,4] FA-NAA is considered to be an inclusion compound formed by van der Waals forces and

hydrophobic interactions between FA and NAA.[4,5] In addition, NAA is recovered from FA-NAA, and the melting point of the recovered NAA is equal to that of the original NAA.[3] In this study, we chose docosanoic acid (C22) as an FA, and prepared C22-NAA crystalline complex (C22-NAA) by dissolving 0.74 g of C22 and 0.32 g of NAA in 60 ml of warm 1,2-dichloroethane and crystallizing at 42 °C. The melting point of thus obtained C22-NAA was 89—91 °C and the stoichiometry was 1:1. No extra free C22 or NAA was mixed in the obtained C22-NAA. (The melting points of C22 and NAA are 78—80 and 128—129 °C, respectively.) C22-NAA is considered to be an inclusion compound composed of $(C22)_n$ and n mol of NAA, although X-ray single crystal analysis has yet to be completed.

First, the transition temperature of C22-NAA was measured by a differential scanning calorimetry (DSC). A small endothermic peak was found at 39.9 °C in the DSC heating curve. The calorie of the peak corresponded to 2.9 kJ mol^{-1}. The heat of transition of octadecanoic acid between polymorphs B and C is 6.0 kJ mol^{-1}.[6] Therefore, the peak corresponds to the transition of the crystal structure of C22-NAA.

Next, the powder X-ray diffraction pattern of C22-NAA was measured under a roughly controlled temperature. Figure 1 shows that the crystal structure of C22-NAA is indeed changed below and above the transition temperature. Furthermore, the peak shift was found above 2 θ angle 15°, although no peak shift was found below 2 θ angle 15°, suggesting that the basic crystal structure is not changed and probably one of the lattice (α, β or γ) may be changed. In addition, the peak shift is large, suggesting that the volume of the host cavity changes largely.

The infrared (IR) spectra of C22-NAA from 27 to 52 °C were obtained. The bands at 3359, 3171 and 1464 cm^{-1} shifted to higher wavenumbers above 42 °C (Fig. 2). Between 27 and 37 °C and between 42 and 52 °C, the spectra are similar. There is a drastic change centered at about 40 °C in the plots. This clearly indicates that there is a crystalline transition centered at about 40 °C. The IR spectra in the 3100—3400 cm^{-1} are the absorption regions where the N-H stretching vibration, the hetero-aromatic C-H stretching vibration and the O-H stretching vibration are overlapped. The band at 1464 cm^{-1} is assigned to the CH_2 scissoring mode. The CH_2 scissoring band is known to be very sensitive to intermolecular interaction and is often used as a key band to check the state of packing of the methylene chain in the crystalline phase.[7] Furthermore, the CH_2 stretching band at 2850 cm^{-1}, which was not given here, was narrow at lower temperatures. This indicates the lower mobility and ordered packing of the methylene chain [8] at a lower temperature. The experimental results indicated that below the transition temperature, the alkyl chain of C22 is

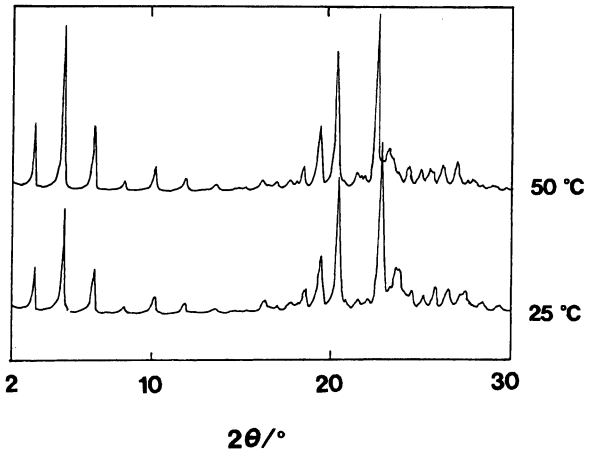

Fig. 1. Powder X-ray diffraction patterns of C22-NAA at 25 and 50 °C. The powder X-ray diffractometer (Rigaku RINT 2100; Rigaku Denki Co., Ltd.) was operated under the following conditions; target Cu, filter Ni, voltage 60 kV, current 300 mV, sampling width 0.020° and scanning speed 6°/min.

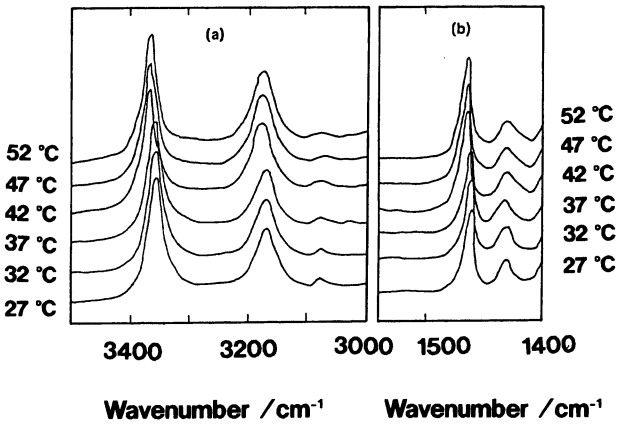

Fig. 2. IR spectra of C22-NAA in the 3100—3400 and 1400—1500 cm^{-1} region at various temperatures. IR spectra were recorded on an FT-IR spectrometer (JASCO Micro Janssen; JASCO Co., Ltd.) with 4 cm^{-1} resolution. A particle of crystalline C22-NAA was placed between two potassium bromide plate, and the IR spectra of dry-state C22-NAA were measured at 27—52 °C with a variable-temperature sample cell. The accuracy in the temperature measurements was ± 0.1 °C. The temperature was raised by 4 °C/min.

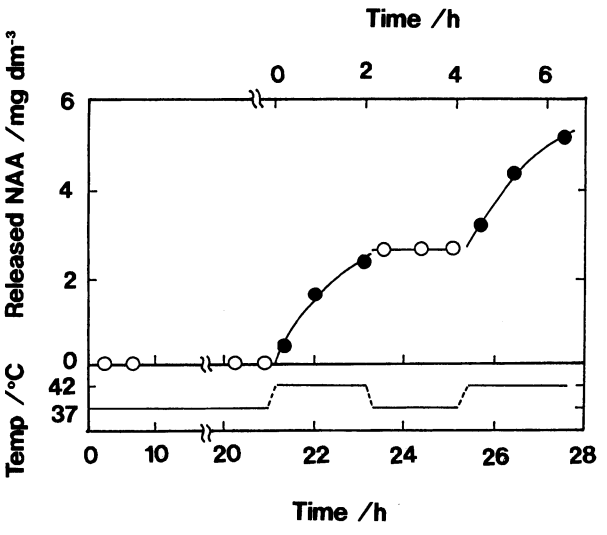

Fig. 3. Release behavior of NAA from C22-NAA by changing temperature 37 (○) ↔ 42 °C (●). C22-NAA with a particle size of 48—60 mesh was supplied for the release test. The release test was carried out by using 38 mg of C22-NAA (this corresponds to 10 mg of NAA) in a JP XII dissolution test apparatus in pH 1.2 JP XII disintegration test medium No. 1. The concentration of released NAA was determined spectrometrically.

orderedly packed: the C22 host cavity is compact and the guest NAA is held tightly. Above the transition temperature, the orderliness is lost, the volume of the C22 host cavity increases largely and the guest NAA cannot be held in the C22 host cavity, and thus NAA is released to the outside of the C22 host cavity.

The release behavior of NAA from C22-NAA was examined in an aqueous solution, whose pH of 1.2 corresponds to the gastric juice of humans. NAA was not released at 37 °C even though the release test was continued for 21 h; NAA was released when the temperature was raised from 37 to 42 °C; and again the release stopped when the temperature was reduced to 37 °C (Fig. 3). We believe that these release characteristics are applicable to a thermo-responsive DDS, though further "in vitro" and "in vivo" experimental research are required.

As mentioned above, the mechanism of thermo-sensitive FA-drug crystalline complex is based on the transition of the crystal structure of FA-drug complex at the transition temperature. The FA-drug crystalline complex has advantages as follows: the response to temperature is rapid because the crystal structure changes quickly at the transition temperature; the transition temperature of the FA-drug crystalline complex can be changed freely by using a proper constituent FA; the content of drug in the complex is uniform because the FA-drug complex has its own stoichiometry. We believe that this method will indeed provide a new tool in this research field and that this concept will be widely applicable in the future.

References

1) H. Katono, K. Sanui, N. Ogata, T. Okano, and Y. Sakurai, Hyomen, **30**, 32 (1992); N. Wada, Y. Kajima, Y. Yagi, H. Inomata, and S. Saito, Langmuir, **9**, 46 (1993).
2) M. Davies and B. Kybett, Trans. Faraday Soc., **61**, 2646 (1965); N. Adriaanse, H. Dekker, and J. Coops, Res. Trav. Chim., **83**, 557 (1964); R. C. F. Schaake, J. C. van Miltenburg, and C. G. de Kruif, J. Chem. Thermodynamics, **14**, 763 (1982); R. C. F. Schaake, J. C. van Miltenburg, and C. G. de Kruif, J. Chem. Thermodynamics, **14**, 771 (1982).
3) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, A. Kaneko, and S. Yokoyama, Vitamins, **62**, 669 (1988).
4) S. Yokoyama, F. Ueda, and T. Fujie, Chem. Pharm. Bull., **39**, 3114 (1991).
5) S. Yokoyama, M. Sakamaki, F. Ueda, A. Kaneko, and T. Fujie, Chem. Pharm. Bull., **40**, 1601 (1992).
6) W. Beckmann, F. Rouquerol, and H. Beckmann, Thermochim. Acta., **66**, 295 (1983).
7) R. G. Snyder, J. Mol. Spectrosc., **7**, 116 (1961); J. Umemura, D. G. Cameron, and H. H. Mantsch, Biochim. Biophys. Acta., **602**, 32 (1980).
8) W. Wang, L. Li, and S. Xi, J. Colloid Interface Sci., **155**, 369 (1993).

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