EFFECT OF ALKYL CHAIN LENGTH OF CONSTITUENT FATTY ACID (FA) ON THE THERMO-SENSITIVITY OF FA-NICOTINAMIDE CRYSTALLINE COMPLEX

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Thermo-sensitive fatty acid (FA)-nicotinamide (NAA) crystalline complexes, FA-NAA, were prepared, and the release of NAA from FA-NAA was investigated in an aqueous medium. The response-temperature of FA-NAA to release NAA was reduced as the carbon number of the constituent FA decreased.

KEYWORDS thermo-sensitive complex; fatty acid; alkyl chain length; thermo-responsive release; drug delivery system

It is important to establish a drug delivery system (DDS) to ensure the high efficacy and minimal side effects of a medicine. We have found that fatty acid (FA)-drug crystalline complex is applicable to a thermo-responsive DDS.[1] The thermo-sensitivity of FA-drug complex is based on the transition of the crystal structure at the transition temperature: the change in the crystal structure of FA-drug complex was confirmed by the powder X-ray diffractometry and the infrared spectroscopy.[1] This is a new concept which is quite different from the conventional method using polymer gel.[2] For the study on the thermo-sensitivity of the FA-drug complex, we have used the docosanoic acid (C22)-nicotinamide (NAA) crystalline complex, C22-NAA, as a model experiment. In pH 1.2 aqueous medium, the release of NAA from C22-NAA was ON-state at 42 °C and OFF-state at 37 °C.[1] In the case of NAA as a drug, controlled release was attained at temperatures close to human body temperature by complexing with C22. It is expected that C22 complexes with the other drugs (for example, antifebriles and anticancer drugs) have different response-temperatures from C22-NAA. In those cases, it is useful to prepare FA-drug complexes which have appropriate response-temperatures by choosing an FA with appropriate alkyl chain length. From these points of view, we prepared octadecanoic acid (C18)-NAA and hexadecanoic acid (C16)-NAA crystalline complexes as a systematic model experiment, and investigated the effect of alkyl chain length of FA on the response-temperature of FA-NAA. Furthermore, whether ON-OFF controlled release of NAA from C18-NAA or C16-NAA will be found was examined in an aqueous medium by repeatedly changing temperature.

C18-NAA was prepared by dissolving 3.25 g of C18 and 1.0 g of NAA in 200 ml of 1,2-dichloroethane and crystallizing at about 20 °C. C16-NAA was prepared by dissolving 2.9 g of C16 and 1.0 g of NAA in 120 ml of 1,2-dichloroethane and crystallizing at about 5 °C. The release test was carried out at 1—32 °C using 30 mg of FA-NAA (this corresponds to 10 mg of NAA) in a JP XII dissolution test apparatus in 500 ml of pH 1.2 JP XII disintegration test medium No. 1; the particulars for the procedure were the same as previously described.[3] The concentration of released NAA was determined spectrometrically.[3] The solubility of NAA in the test medium is sufficiently large even at 1 °C (solubility of NAA > 1 g/ml), and the velocity of dissolution is sufficiently large (the velocity of dissolution >> the velocity of release). So the velocity of dissolution does not affect the velocity of release.

When the release of NAA from C18-NAA was examined at temperature intervals of 5 °C, it was found that more than 80 % was released at temperatures above 27 °C, while NAA was scarcely released at temperatures below 22 °C. The percentage of released NAA from C16-NAA was more than 82 % above 15 °C, while NAA was scarcely released below 5 °C. The

relationship between the percentage of released NAA and temperature is shown in Fig. 1. The result for C22-NAA [1] is also shown in Fig. 1 to make it easier to compare with the results for C18-NAA and C16-NAA. As can be seen in Fig. 1, the critical temperature at which NAA begins to release was reduced as the carbon number of constituent FA decreased. This phenomenon is reasonable based on the fact [4] that the transition temperature of alkanoic acid decreases with decreasing carbon number of alkanoic acid.

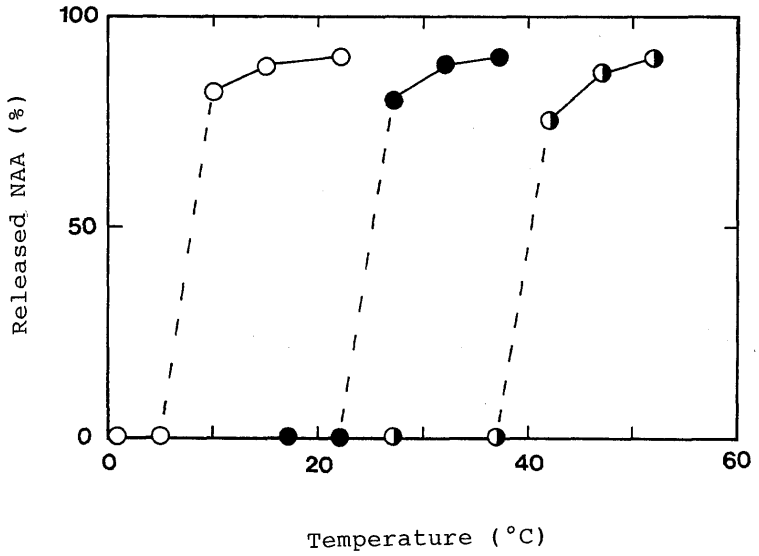

Fig. 1. Relationship between Percentage of Finally Released NAA and Temperature
FA-NAA: ○, C16-NAA; ●, C18-NAA; ◑, C22-NAA [1]

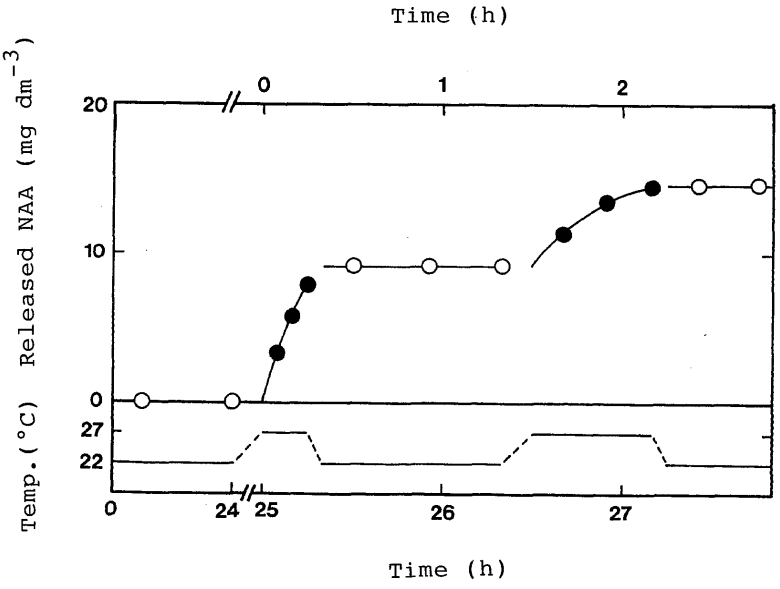

Fig. 2. Release Behavior of NAA from C18-NAA with Changing Temperature 22 ⟷ 27 °C

Next, the release behaviors of NAA from C18-NAA and C16-NAA were repeatedly measured at 22 ⟷ 27 °C and 5 ⟷ 10 °C, respectively. The results are shown in Figs. 2 and 3. As can be seen in Fig. 2, NAA was not released from C18-NAA at 22 °C even though the release test was continued for 24 h; release began when the temperature was raised from 22 °C to 27 °C, and again stopped when the temperature was reduced to 22 °C. As Fig. 3 shows, NAA was not released from C16-NAA at 5 °C even though the release test was continued for 24 h; it was released when the temperature was raised from 5 °C to 10 °C, and again the release stopped when the temperature was reduced to 5 °C. The released NAA is not re-included in the complex (FA host structure [5]) when the temperature is reduced. C18-NAA and C16-NAA indicate a thermo-responsible ON-OFF controlled release. The release of NAA from FA-NAA composed of FA with shorter alkyl chain length was faster. Therefore, a small amount of NAA was released from C16-NAA when the temperature was reduced to a given temperature.

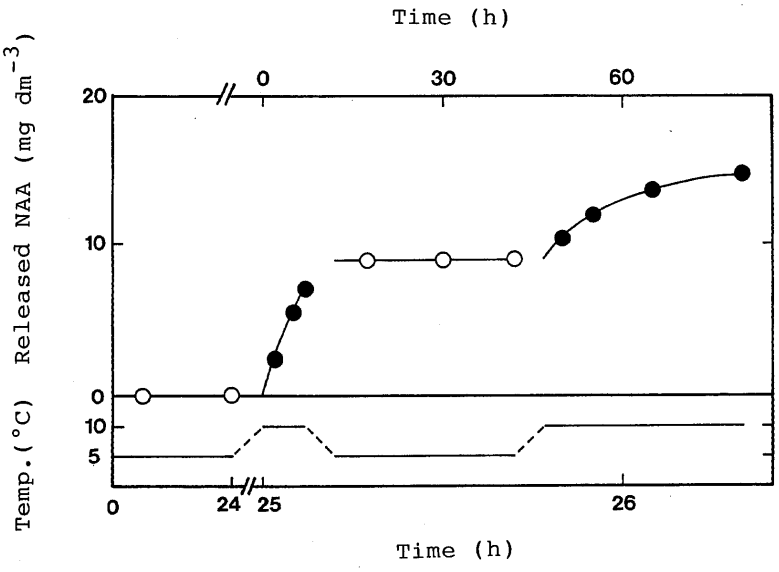

Fig. 3.
Release Behavior of NAA from C16-NAA with Changing Temperature 5 ⟷ 10 °C

As described above, C22-NAA, C18-NAA and C16-NAA showed an ON-OFF controlled release at each response-temperature. The response-temperature of FA-NAA was reduced as the carbon number of constituent FA decreased. It is suggested that the response-temperature of FA-drug crystalline complex will be regulated to an appropriate temperature by choosing an appropriate FA.

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