THE TEMPERATURE-RESPONDENT RELEASE BEHAVIOR OF A NEW CRYSTALLINE COMPLEX, DOCOSANOIC ACID-NICOTINAMIDE

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A new crystalline complex composed of docosanoic acid and nicotinamide (NAA) was prepared. The release of NAA from the complex in an aqueous medium was found to be ON-state above 37 °C and OFF-state below 37 °C, suggesting that the release behavior is applicable to a temperature-respondent drug delivery system.

KEYWORDS docosanoic acid; nicotinamide; complex; temperature-respondent release; drug delivery system

It has already been reported [1] that fatty acids (FA) whose carbon number is 12—18 form crystalline complexes with nicotinamide (NAA) and that the complex FA-NAA is a clathrate or an inclusion compound.[2] Furthermore, it has been found [3] that the release behavior of NAA from the octadecanoic acid (C18)-NAA equimolar complex in pH 1.2 aqueous medium changes largely at 22—27 °C. This is due to the transition [3,4] of the crystal structure of C18-NAA which has been prepared at 35 °C, as in the transition of FA between B polymorph and C polymorph. So it is expected that the transition temperature will be raised, if FA with a longer alkyl chain is used to prepare the FA-NAA complex. From these points of view, we prepared the docosanoic acid (C22)-NAA equimolar complex, and the release of NAA from C22-NAA was measured at various temperatures. Furthermore, the applicability of C22-NAA to a temperature-respondent drug delivery system was investigated. An interesting phenomenon was observed. So the result will be present in this paper.

C22-NAA was prepared by dissolving 0.74 g of C22 and 0.32 g of NAA in 60 ml of 1,2-dichloroethane and crystallizing at 40 °C. The melting point of the thus obtained complex was 89—91 °C and the stoichiometry was 1:1. C22-NAA whose particle size is 48—60 mesh [5] was supplied for the release test. The release test was carried out at various temperatures 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 and 6.8 JP XII disintegration test medium No. 1 and 2; the particulars for the procedure were the same as previously described.[5] The concentration of released NAA was determined spectrophotometrically, as previously described.[5] The solubility of NAA in the test medium is sufficiently large at room temperature (solubility of NAA $>$ 1 g/ml), and the velocity of dissolution is sufficiently large (the velocity of dissolution $\gg$ the velocity of release).[5] So the velocity of dissolution does not affect the velocity of release.

When the release of NAA from C22-NAA was examined at temperature intervals of 10 °C from 37 °C (27—57 °C), it was found that NAA released more than 90 % at temperatures above 47 °C, while NAA scarcely released at temperatures below 37 °C. So the release behavior at pH 1.2 and 6.8 was repeatedly measured at 37 $\leftrightarrow$ 47 °C; the results are shown in Figs. 1 and 2. The ordinate of the figure shows graduated amount of released NAA in units of mg/l. As can be seen in Figs. 1 and 2, NAA is released at 47 °C; the release stops when the temperature is reduced to 37 °C, and NAA is released again when the temperature is raised from 37 °C to 47 °C. Similar patterns with regard to the temperature-respondent release were found in the medium of both pH 1.2 and 6.8, although the release at pH 6.8 was faster than that at pH 1.2.

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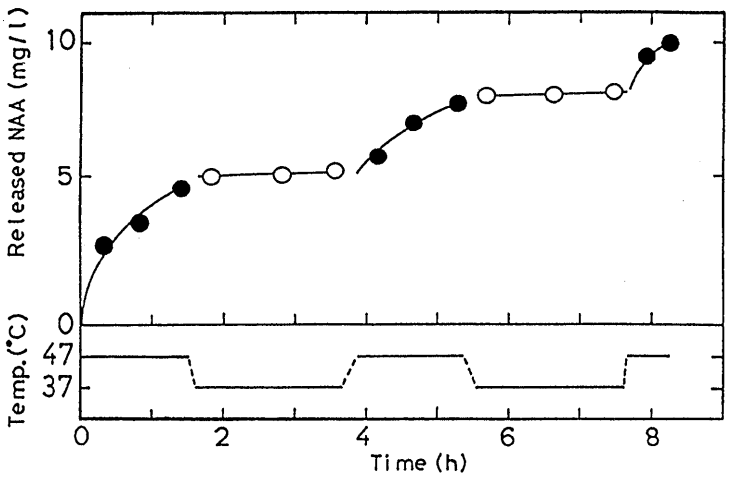
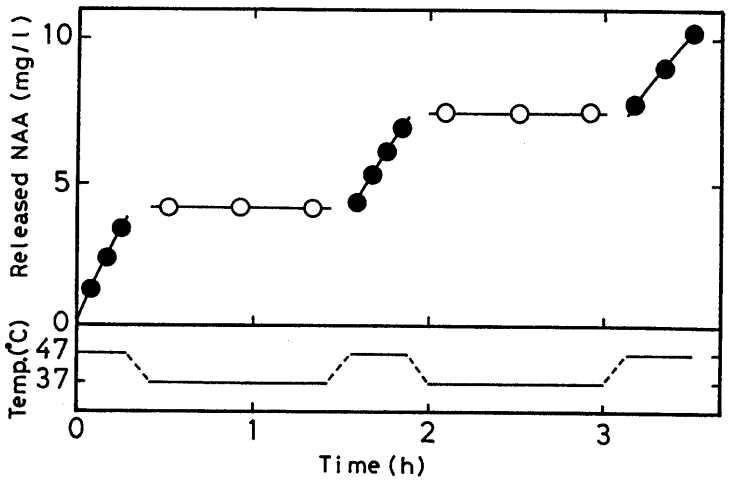


Fig. 1
Release Behavior of NAA from C22-NAA by Changing Temperature
pH: 1.2

Fig. 2
Release Behavior of NAA from C22-NAA by Changing Temperature
pH: 6.8



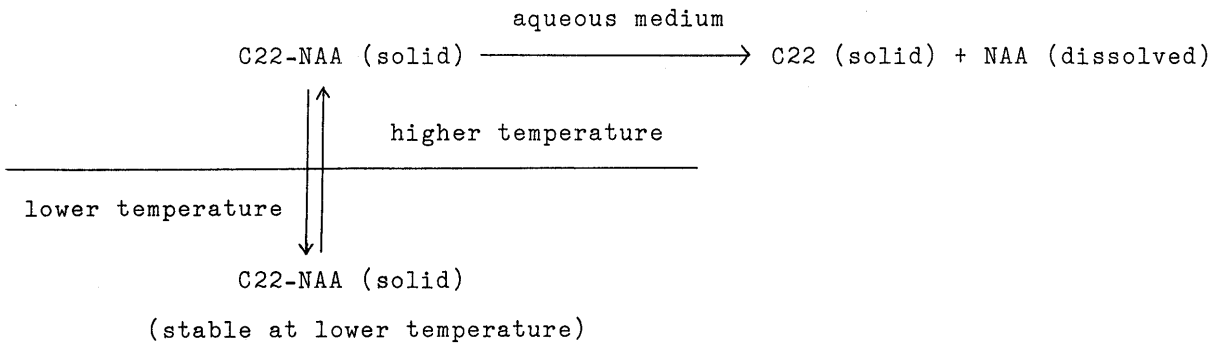


Chart 1. Scheme for the Release of NAA from C22-NAA

The release of NAA from C22-NAA is described as shown in Chart 1. C22 is insoluble in an aqueous medium at least in the acidic—neutral region. C22 maintains the host structure after NAA has been released.

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Last, another C22-NAA crystalline complex, as described in Chart 1, which is stable at lower temperatures, was prepared by dissolving C22 and NAA in 1,2-dichloroethane and crystallizing at 10 °C; the melting point of the thus obtained complex was 91—93 °C. The release behavior was repeatedly examined within a narrower temperature range of 36↔42 °C, and the result is shown in Fig. 3. As can be seen in Fig. 3, NAA was not released at 36 °C even though the release test was continued for 21 hr; NAA was released when the temperature was raised from 36 °C to 42 °C, and again the release stoped when the temperature was reduced to 36 °C.

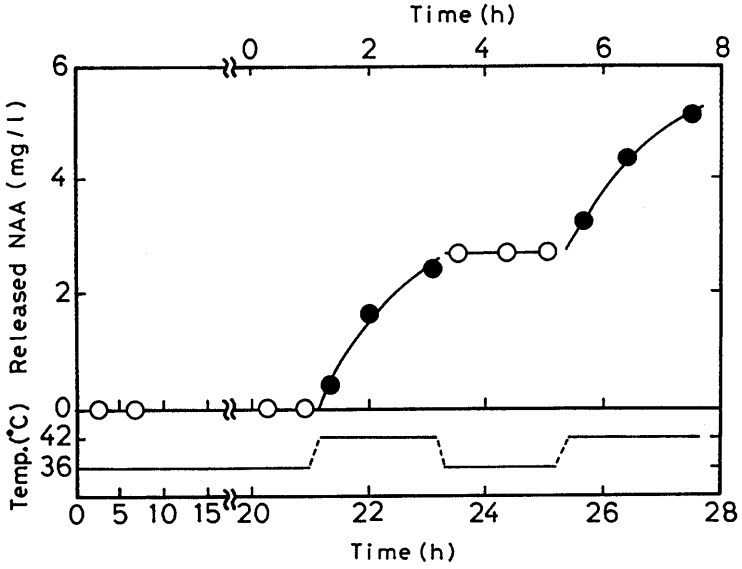

Fig. 3
Release Behavior of NAA from Another Stable C22-NAA by Changing Temperature
pH: 1.2

The temperature-respondent release behavior as observed for C22-NAA might be applicable to a drug delivery system (DDS). For studies of the temperature-respondent DDS, polyacrylamide as a polymer has been used.[6] This is based on the properties of polymer, swelling and contraction with changing temperature. Furthermore, it has been reported [6] that the release of drug from the polyacrylamide complex is OFF-state at 10 °C and ON-state at 30 °C. The release characteristics of C22-NAA (with release of drug controlled by a temperature closer to body temperature) may be useful as a temperature-respondent DDS, especially for antifebriles.

The release behavior of C22-NAA shown in Figs. 1—3 is considered to be due to the transition of the crystal structure near 37 °C. So we shall carry out a thermokinetic analysis of C22-NAA by the DSC-FT/IR method to clarify these phenomena in parallel with the X-ray single crystal analysis.

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(Received July 1, 1992)

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