

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 >> 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 ↔ 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.

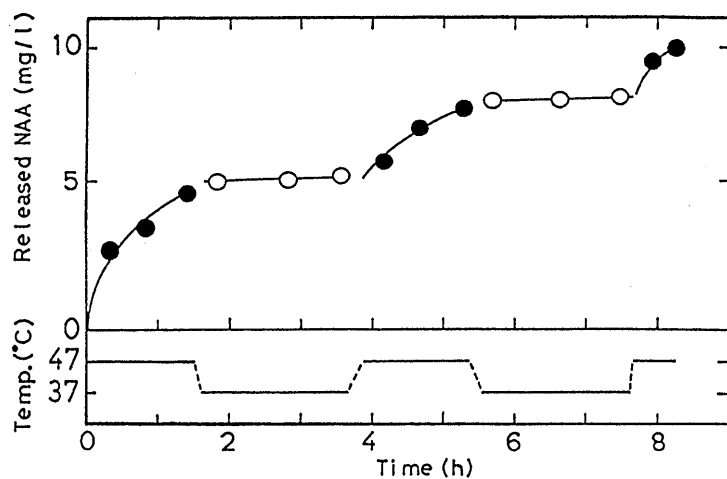


Fig. 1

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

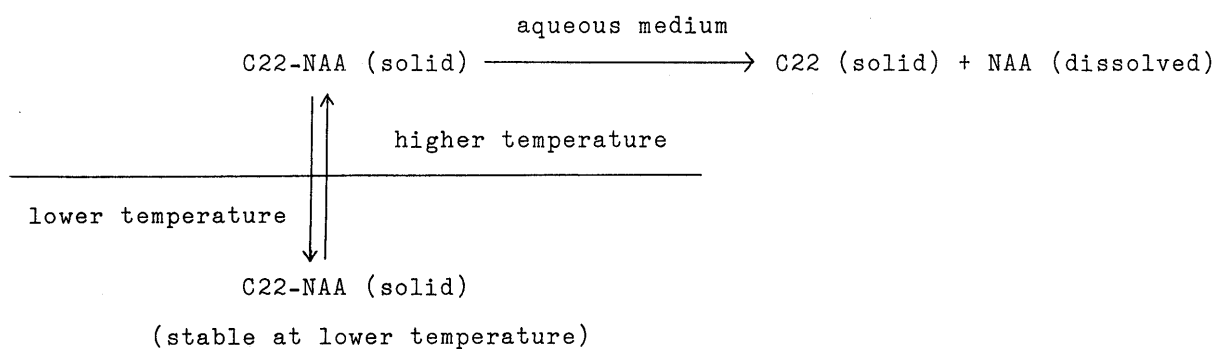
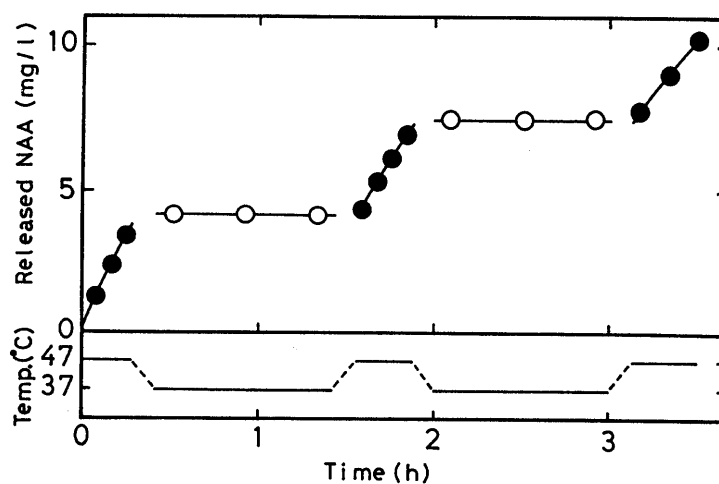


Chart 1. Scheme for the Release of NAA from C22-NAA

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.

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 stopped when the temperature was reduced to 36°C.

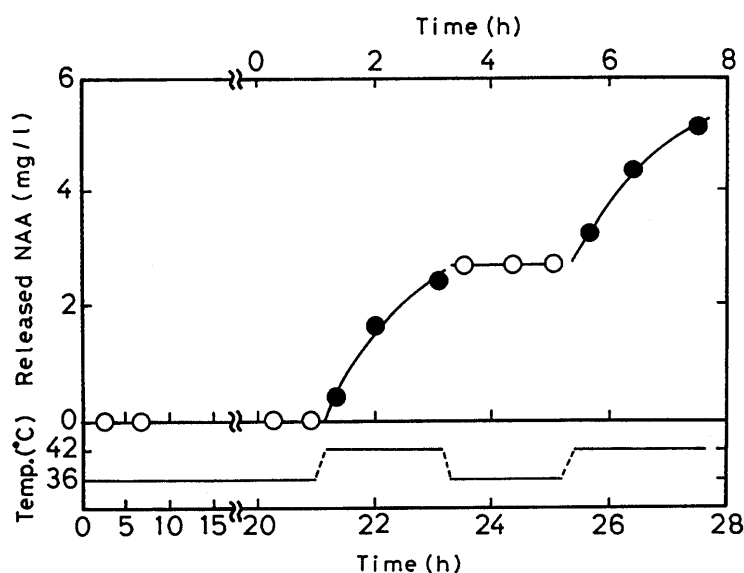


Fig. 3
Release Behavior of NAA from
Another Stable C22-NAA by
Changing Temperature
pH: 1.2

The temperature-responsive release behavior as observed for C22-NAA might be applicable to a drug delivery system (DDS). For studies of the temperature-responsive 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 reported⁶⁾ 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-responsive 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.

REFERENCES

- 1) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, A. Kaneko, and S. Yokoyama, *Bitamin*, **62**, 669 (1988).
- 2) S. Yokoyama, M. Sakamaki, F. Ueda, A. Kaneko, and T. Fujie, *Chem. Pharm. Bull.*, **40**, 1601 (1992).
- 3) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 1634 (1991).
- 4) S. Yokoyama, F. Ueda, and T. Fujie, *Bull. Chem. Soc. Jpn.*, **64**, 3168 (1991).
- 5) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 3075 (1991).
- 6) H. Katono, K. Sanui, N. Ogata, T. Okano, and Y. Sakurai, *Hyomen*, **30**, 32 (1992).

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