PH-SENSITIVE DOCOSANOIC ACID-NICOTINAMIDE COMPLEX, AND ITS APPLICABILITY TO A PH-RESPONSIVE DRUG DELIVERY SYSTEM

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The release of nicotinamide (NAA) from docosanoic acid (C22)-NAA complex was measured in pH 1.2—6.8 aqueous media. The release of NAA was ON-state below pH 6.2 and OFF-state at pH 6.8, suggesting that the release behavior is applicable to a pH-responsive drug delivery system.

KEYWORDS pH-sensitive complex; docosanoic acid; nicotinamide; pH-responsive release; drug delivery system

It is becoming more and more important to establish a drug delivery system for the purpose of high efficacy and minimum side effects. We have already reported that docosanoic acid (C22)-nicotinamide (NAA) complex, C22-NAA, is applicable to a thermo-responsive drug delivery system (DDS): NAA was not released from C22-NAA below 37 °C in the JP XII disintegration test medium No. 1, while NAA was released when the temperature was raised from 37 °C to 42 °C.[1] The mechanism for the thermo-sensitivity of C22-NAA[1] is completely different from the conventional polymer-drug gel.[2] At the same time, pH-sensitive liposome has been designed[3] to target areas of the body, such as inflammation or malignant transformation, where the local pH is below normal. In the present situation, discovering a new pH-sensitive compound has high academic value. In addition, fatty acid (FA)-drug complex may become more useful in the pharmaceutical field, if C22-NAA is sensitive to both temperature and pH. From these points of view, the release of NAA from C22-NAA was measured in pH 1.2—6.8 aqueous media, and the applicability of C22-NAA to a pH-responsive DDS was investigated.

C22-NAA was prepared by dissolving C22 and NAA in 1,2-dichloroethane and crystallizing at 10 °C.[1] C22-NAA whose particle size is 48—60 mesh[1] was supplied for the release test. The release test was carried out in pH 1.2—6.8 aqueous media by using a JP XII dissolution test apparatus (modified rotating basket method whose mesh size is 100), where the pH 1.2 and 6.8 aqueous media are the JP XII disintegration test media No. 1 and 2, respectively, and the others whose pH 3.0—6.2 are phosphate buffers. 38 mg of C22-NAA (this corresponds to 10 mg of NAA) was used in the test. The concentration of released NAA was determined spectrometrically. The solubility of NAA in the pH 1.2—6.8 test medium is sufficiently large at room temperature, and the velocity of dissolution is sufficiently larger than that of release. So the velocity of dissolution does not affect the velocity of release.

The release behavior of NAA from C22-NAA at pH 1.2—6.8 and 41 °C is shown in Fig. 1, and the percentage of finally released NAA is plotted against pH in Fig. 2. NAA released more than 90 % at pH 3.0—6.2 and about 70 % at pH 1.2, while NAA scarcely released at pH 6.8 and 41 °C, although NAA released about 80 % at 47 °C and the release at pH 6.8 was faster[1] than that at pH 1.2. One reason for this phenomenon is the activation energy (E^*) for the release: E^* at pH 6.8 is about 3-fold larger than that at pH 1.2,[4] and the Arrhenius plots for the release at pH 1.2 and 6.8 intersect at about 44 °C;[4] hence the release at pH 6.8 is faster than that at pH 1.2 above 44 °C and the release at pH 1.2 is faster than that at pH 6.8 below 44 °C.

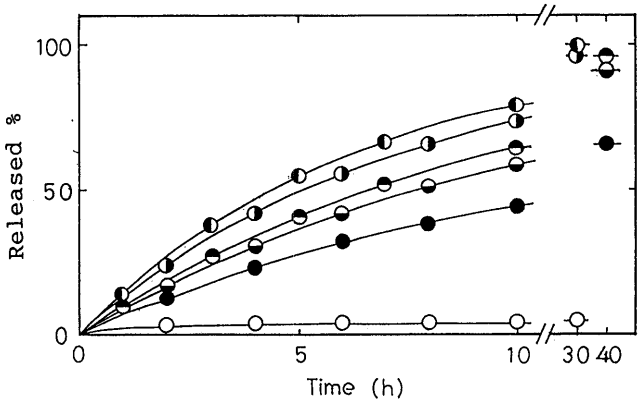

Fig. 1.
Effect of pH on the Release of NAA from C22-NAA
pH: ●, 1.2; ◑, 3.0; ◐, 4.0; ◓, 5.0; ◒, 6.2; ○, 6.8.
Temperature: 41 °C.

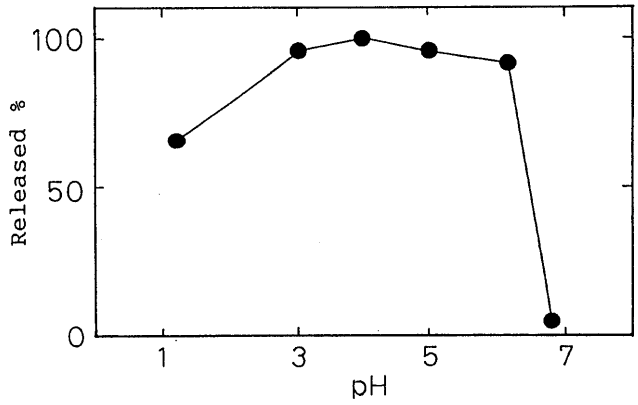

Fig. 2.
Relationship between Percentage of Finally Released NAA and pH
Temperature: 41 °C.

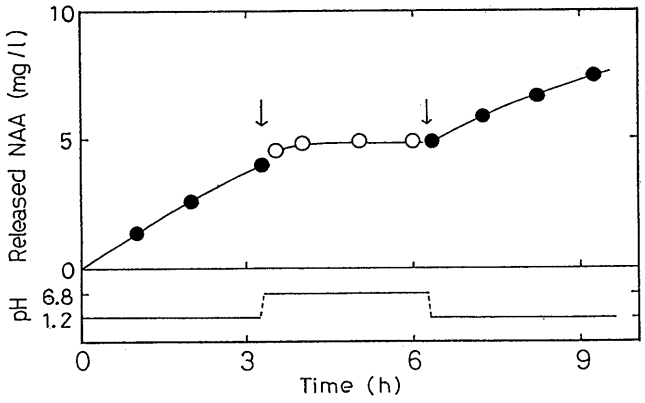

Fig. 3.
Release Behavior of NAA from C22-NAA by Changing pH 1.2 ⟷ 6.8
Temperature: 41 °C.

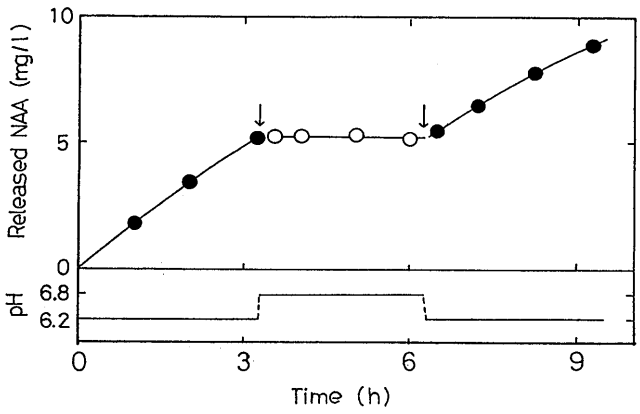

Fig. 4.
Release Behavior of NAA from C22-NAA by Changing pH 6.2 ⟷ 6.8
Temperature: 41 °C.

Next, a pH-exchanging experiment was carried out using two vessels: at an appropriate time, the basket was pulled out of the first test medium and then immersed in the second test medium. The result at pH 1.2 ⟷ 6.8 is shown in Fig. 3. The ordinate of the figure shows graduated amount of released NAA in units of mg/l. As can be seen in Fig. 3, NAA is released at pH 1.2; the release roughly stops when the pH is raised to 6.8, and NAA is released again when the pH is reduced from 6.8 to 1.2. A little leak at pH 1.2 → 6.8 is considered to be due to the fact that the pH change surrounding C22-NAA passes through the pH 3—6 region where the release of NAA is faster. Next, the release behavior was measured at pH 6.2 ⟷ 6.8, and the result is shown in Fig. 4. NAA was released at pH 6.2; the release stopped when the pH was raised to 6.8, and NAA was released again when the pH was reduced from 6.8 to 6.2. ON-OFF control for the release of drug was achieved at a narrow pH range. The pH 1.2 and 6.8 correspond to the gastric and the intestine pH of humans, respectively. So the release characteristic shown in Fig. 3 suggests the release of drug in the stomach and a stop to release in the small intestine. Under pathological conditions, such as malignant transformation, the local pH is reduced below normal: the pH of the fluid around the tumor is about 6.2.[5] In the present state, it is still too early for us to suggest the applicability of FA-drug complex to a pH-responsive DDS (OFF-state at pH 6.8 and ON-state at pH 6.2) for anticancer drugs because of insufficient "in vitro" data and lack of "in vivo" data. We shall carry out further research. We are now examining the effect of the constituent FA and the constituent drug of the FA-drug complex on pH where the drug begins to release.

We have not yet obtained enough information on the mechanism of the pH-responsive release of C22-NAA (either/neither change in the structure of C22-NAA or/nor activation energy for the release of NAA). Nevertheless C22-NAA was found to be sensitive to pH. FA-drug complex may be applicable not only to a thermo-responsive DDS[1] but also to a pH-responsive DDS, though extensive preliminary examinations in experimental animals will be required.

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