RELEASE OF NICOTINAMIDE (NAA) FROM THERMO-SENSITIVE FATTY ACID-NAA COMPLEX COATED WITH CELLULOSE ACETATE PHTHALATE

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The release of nicotinamide (NAA) from the thermo-sensitive octadecanoic acid complex (C18-NAA) coated with cellulose acetate phthalate was investigated in pH 1.2 and 6.8 aqueous media. No release of NAA from the enteric-coated C18-NAA was found at pH 1.2, while NAA was released at pH 6.8 in response to the temperature. It was confirmed that the thermo-sensitivity of C18-NAA is not affected by the enteric-coating treatment.

KEYWORDS thermo-sensitive complex; enteric coating; drug delivery system; fatty acid; nicotinamide

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.[1] For the study of the thermo-sensitive FA-drug complex, we have used the fatty acid-nicotinamide (NAA) crystalline complex, FA-NAA, as a model experiment. In pH 1.2 aqueous medium, the release of NAA from docosanoic acid (C22)-NAA was in the ON-state at 42 ℃ and in the OFF-state at 37 ℃; [1] the release of NAA from octadecanoic acid (C18)-NAA was in the ON-state at 27 ℃ and in the OFF-state at 22 ℃; [2] and the response-temperature of FA-NAA to release of NAA was reduced as the carbon number of the constituent FA decreased.[2] On the other hand, thermo-sensitive polymer gel [3] and pH-sensitive liposome [4] have been designed. If FA-NAA can be enteric-coated, thermo-sensitive FA-drug complex will become more useful in the pharmaceutical field. From these points of view, FA-NAA was enteric-coated, the release of NAA from the enteric-coated FA-NAA was measured in aqueous media, and whether the thermo-sensitivity of FA-NAA is affected by the enteric-coating was investigated.

In this study, C18-NAA, which releases NAA faster than C22-NAA, was used as a model experiment for the purpose of reducting experimental time. 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 ℃, as previously described.[2] The particle size of 48–60 mesh of C18-NAA was taken for the experiment. Cellulose acetate phthalate (CAP) was used as an enteric-coating agent. CAP was dissolved in acetone, and 5 *w/v*% CAP solution was prepared. 1 ml of 5 *w/v*% CAP solution was admixed with 10 mg of C18-NAA, and the CAP-coated C18-NAA was obtained as a thin film having a diameter of 15 mm by casting and evaporating acetone at room temperature. The release

test was carried out in triplicate in a JP XII dissolution test apparatus (rotating basket method) in 500 ml of pH 1.2 or pH 6.8 JP XIIdisintegration test medium No. 1 or 2, as previously described.[5] C18-NAA and C18 are insoluble in the test medium, and released NAA is dissolved in the test medium. The concentration of released NAA was determined spectrometrically.[6] We have confirmed that about 90 % of NAA is released from C18-NAA within 30 min in the pH 1.2 aqueous medium and within 20 min in the pH 6.8 aqueous medium at 37 ℃.

First, the acid-proof test for the CAP-coated C18-NAA was carried out in the pH 1.2 aqueous medium at 37 ℃. No dissolution of CAP and no release of NAA from the CAP-coated C18-NAA were found at least for 2 h defined by JP XII. The CAP-coated C18-NAA passed the pH 1.2 resistance test.

Next, the release test of NAA from the CAP-coated C18-NAA was carried out at pH 6.8 and 37 ℃ following the first test at pH 1.2 and 37 ℃. The basket was pulled out of the first test medium and then immersed in the second test medium. The result is shown in Fig. 1. The experimental errors of three measurements (the difference between minimum and maximum values) are shown by bars in the figure. Where no bar is shown, it lies within the symbol. After a short lag-time, NAA began to release at pH 6.8. The release rate was accelerated after CAP had been dissolved, and more than 90 % of NAA was released within 1 h. In the case where 20 *w/v*% CAP was used, longer time was required to dissolve CAP alone, suggesting the retardation of pharmacological efficacy of NAA. Thus 5 *w/v*% of CAP is suitable for the coating.

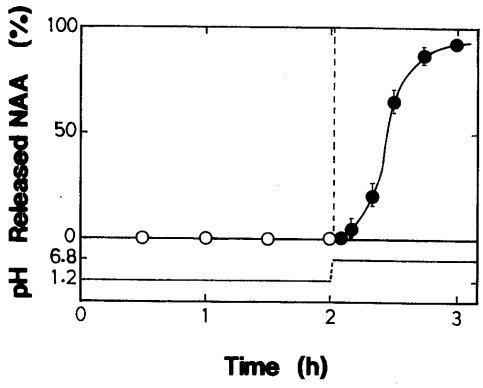

Fig. 1. Release of NAA from CAP-Coated C18-NAA at 37 ℃
pH: ○, 1.2 (acid-proof test); ●, 6.8.

If the thermo-sensitivity of C18-NAA is not affected by the enteric-coating treatment, no release of NAA should be found below the transition temperature of C18-NAA after CAP surrounding C18-NAA has been dissolved. Last, a temperature-exchanging experiment was repeatedly carried out. In addition, the blank dissolution test of CAP without C18-NAA was carried out in parallel with the release test of NAA from the CAP-coated C18-NAA. CAP in the blank test and CAP in the coated C18-NAA were dissolved within 1 h at pH 6.8 and 20 ℃: the blank solution became a clear liquid, while the test solution remained small crystalline particles. The melting point of the residue in the test solution coincided with that of C18-NAA. At pH 6.8 and 20 ℃, no release of NAA from C18-NAA was found. The result at temperature 20 ⇄ 37 ℃ is shown in Fig. 2. When the temperature was raised from 20 to 37 ℃, NAA was released from C18-NAA, and the release

stopped when the temperature was reduced to 20 ℃. These results clearly indicate that the thermo-sensitivity of C18-NAA is not affected by the enteric-coating treatment.

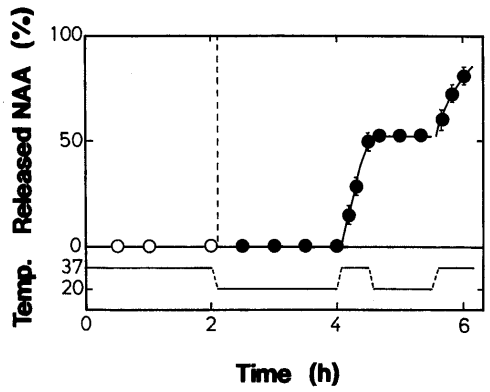

Fig. 2. Release Behavior of NAA from CAP-Coated C18-NAA with Changing Temperature
20⇄37 ℃
pH: ○, 1.2 (acid-proof test); ●, 6.8.

The release characteristics of the enteric-coated C18-NAA suggest that drug is not released from enteric-coated fatty acid-drug complex in the stomach and is released in the small intestine in response to the temperature. The response-temperature can be regulated to an appropriate temperature by choosing an appropriate FA.[2] If C22-NAA (the release of NAA is in the ON-state at 42℃) is enteric-coated, NAA will be released in the small intestine under a febrile condition: the release characteristic may be useful for anticancer drugs (for the cancer in the small intestine) in combination with thermotherapy, although further research is required. In addition, if the enteric-coated icosanoic acid (C20)-NAA is prepared, NAA may be released in the small intestine at 37℃, although C20-NAA has not yet been prepared because of the exceptionally high cost of C20.

In conclusion, the thermo-sensitivity of C18-NAA was not affected by the enteric-coating treatment. The release rate of NAA from the enteric-coated C18-NAA was slightly later than that from the original (non-treatment) C18-NAA. This is considered to be caused by the secondary aggregation of the C18-NAA particle during the enteric-coating. We are sure that it is possible to solve this problem by spray granulation method with a coatingpan. We believe this study will be the basis for the manufacture of enteric-coated granules of thermo-sensitive fatty acid-drug complex.

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