Release of Nicotinamide from Fatty Acid–Nicotinamide Equimolar Complexes[1)]

Shoko YOKOYAMA,*[,a] Fumio UEDA,[b] and Tadao FUJIE[a]

Kyoritsu College of Pharmacy,[a] 1–5–30, Shibakoen, Minato-ku, Tokyo 105, Japan and Research Laboratory, Kawai Seiyaku Co., Ltd.,[b] 6–3–5, Nakano, Nakano-ku, Tokyo 164, Japan. *Received April 19, 1991*

The release behavior of nicotinamide (NAA) from fatty acid (FA)–NAA equimolar complexes was examined in a JP XI dissolution test apparatus in JP XI disintegration test medium No. 1 (pH 1.2) at 37 °C where the carbon number of FA is 14—18. The time required for 50% or 80% of NAA to release (T_{50} or T_{80}) was measured, and the effect of the constituent FA on T_{50} or T_{80} was investigated. The values of T_{50} or T_{80} for FA–NAA formed with odd-numberd FA were larger than those for FA–NAA formed with even-numbered FA whose alkyl chain length is one more carbon number longer, though the values of T_{50} of T_{80} increased rather regularly with an increase of the alkyl chain length for only even-numbered or odd-numbered FA. The values of T_{50} and T_{80} for FA–NAA formed with heptadecanoic acid (C17–NAA) were about 36 and 102 min, respectively, suggesting that C17–NAA may be applicable to the preparation of a sustained-release drug formulation.

Keywords nicotinamide; fatty acid; complex; equimolar complex; release; sustained-release

Nicotinamide (NAA) is well-known as being biosynthesized to nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate in organisms. In addition, NAA is known as an antipellagra substance. 25—200 mg/d of NAA is applied to clinical trials for pellagra, 0.5—1 g/d of NAA is applied in serious cases.

The side effects of NAA are weaker than that of nicotinic acid which have a similar therapeutic efficacy. However, side effects such as a disturbance of the stomach and intestine and a decline of hepatic function is generated when large doses of NAA are administered. Furthermore, *in vivo* utilization of glucose is disturbed by the administration of large doses of NAA. These side effects are caused by a sudden increase of the serum concentration of nicotinic acid or NAA. For the purpose of suppression of the side effects, a sustained-release dosage of nicotinic acid derivatives is now in the process of development: for example, a patent with a slow-release drug product containing a nicotinic acid derivative as the major component and a water soluble polymer as the carrier was reported.[2)]

On the other hand, it has been reported[3)] that NAA forms a crystalline complex with a fatty acid (FA) whose molar ratio of FA to NAA is 1 : 1, FA–NAA. Such a complex formed with FA and a water soluble drug has been found for thiamine disulfide (TDS), and the release behavior of TDS from the complex has also been examined.[4)] In the studies, it is suggested that the complexes formed with FA may be applicable to the preparation of a sustained-release drug formulation. FA–NAA is, therefore, expected as a sustained-release drug. It is required to know the release behavior of NAA from FA–NAA for pharmaceutical applications. From these points of view, the release rates of NAA from FA–NAA were determined. The effect of particle size on the release rate has been investigated,[4a)] and the particle size of 48—60 mesh is suggested to be suitable at least for a subsequent study. The particle size of FA–NAA in this study was, therefore, set at a limit of 48—60 mesh.

Experimental

Materials NAA, tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17) and octadecanoic acid (C18) were the same as those used previously.[3)] The melting points of NAA, C14, C15, C16, C17 and C18 are 128—129, 53—55, 52—54, 64—65, 60—62 and 69—71 °C, respectively. FA–NAA were prepared as previously described.[3)] Purities of FA–NAA were examined with a melting point-measuring apparatus equipped with a microscope (×100), and it was confirmed that no extra free FA and/or NAA was present. The melting points of C14–NAA, C15–NAA, C16–NAA, C17–NAA and C18–NAA were 73—75, 77—79, 79—80, 80—82 and 83—85 °C, respectively. Crystals of FA–NAA were passed through 48 and 60 mesh sieves, and the particle of 48—60 mesh was collected.

Measurement of Release Rate The release of NAA from FA–NAA was tested as previously described[4)] in a JP XI dissolution test apparatus (paddle method) in 500 ml of JP XI disintegration test medium No. 1 (pH 1.2) at an agitation speed of 200 rpm at 37 °C. About 29—33 mg of each FA–NAA (this corresponds to about 10 mg of NAA) was used in the test. Aliquots of 5 ml of sample solution were withdrawn at appropriate time intervals, and the volume was kept constant by adding the same volume of fresh medium at the same temperature. The sample solution was filtered immediately through a glass filter, and the absorbance was determined. FA is insoluble in aqueous acidic solvent, and a solid residue remains after NAA is released. All release experiments were carried out at least in triplicate and the results were highly reproducible. The release rates are shown as the times required for 50% or 80% of NAA to release (T_{50} or T_{80}).

Quantitative Analysis of NAA The concentration of NAA was determined spectrophotometrically at a wavelength of 261 nm. The relationship between concentration and absorbance was found to obey Beer's law, and the molar absorptivity (ε_{261}) was obtained as $5.80 \times 10^3\ mol^{-1}\ dm^3\ cm^{-1}$.

Solubility of NAA NAA dissolved immediately in the acidic test medium. It is considered that the dissolution rate of NAA is negligible to determine the release rate of NAA from FA–NAA.

Results and Discussion

Effect of FA on the Release Rate of NAA The effect of the constituent FA on the release behavior of NAA from FA–NAA was examined, and the results are shown in Fig. 1. The percentages of released NAA were calculated with respect to the total concentration of NAA which is theoretically contained in the 1 : 1 complex, FA–NAA. As can be seen in Fig. 1, NAA was released to about 95% from C14–NAA and about 88% from C15–NAA—C18–NAA, while TDS was released[4)] to the extent of about 100% from all $(FA)_6$ (TDS).

Recently, we have confirmed that the equimolar complex FA–NAA consists of six molecules of FA and six molecules of NAA. The results were reported promptly.[5)] Furthermore, it was suggested[6)] that six molecules of NAA are included in the $(FA)_6$ host structure which consists of six molecules of FA. On the other hand, one molecule of TDS is included in $(FA)_6$.[4b)] One reason for the difference in the released percentage of drug between FA–NAA and

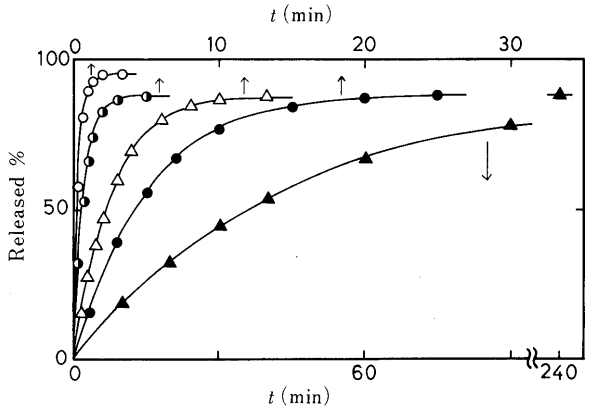

Fig. 1. Release Behavior of NAA from FA–NAA with Varying Alkyl Chain Lengths

Carbon numbers in FA: ○, 14; ◑, 16; ●, 18; △, 15; ▲, 17. Particle size: 48—60 mesh. Temperature: 37 °C.

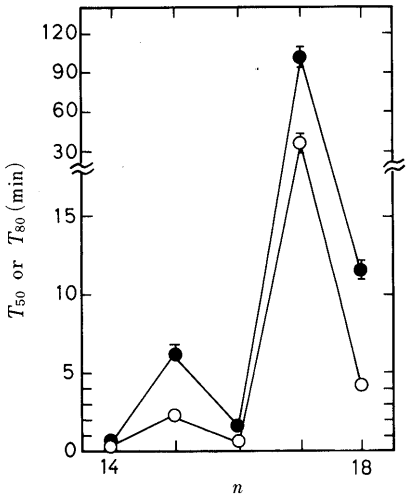

Fig. 2. Effect of FA on the Release Rate (T_{50} or T_{80}) of NAA from FA–NAA

Time required for 50% or 80% of NAA to release; ○, T_{50}; ●, T_{80}. Particle size: 48—60 mesh. Temperature: 37 °C.

$(FA)_6$(TDS) may be related to the compositions of FA–NAA and $(FA)_6$(TDS).

The values of T_{50} and T_{80} are plotted against the carbon numbers of FA, n, in Fig. 2. To indicate the variation in measured values, the difference between minimum and maximum values is shown by a bar in Fig. 2. Where no bar is shown, it lies within the symbol. The relationship between release time (T_{50} or T_{80}) and n was a zig-zag one, though the values of T_{50} or T_{80} increased rather regularly with an increase of n for only even-numbered or odd-numbered FA. This is a similar tendency to that reported for the release of TDS from $(FA)_6$ (TDS).[4] The delayed release rate for FA–NAA composed of odd-numbered FA may be considered to be due to that the interaction between odd-numbered FA and NAA is stronger than that between even-numbered FA and NAA. This is also reflected in the melting points of FA–NAA: the melting points of FA–NAA formed from even-numbered FA are about 15—20 °C higher than those of the original even-numbered FA, while the melting points of FA–NAA formed from odd-numbered FA are about 20—25 °C higher than those of the original odd-numbered FA. Furthermore, this is related to that the crystal structure of FA–NAA formed with odd-numbered FA is a little different from that formed with even-numbered FA.[3,6] In addition, the phenomenon that the release rate decreases as the carbon number of either even-numbered or odd-numbered FA increases is considered to be related to the hydrophobic character of FA. Namely, the hydrophobicity of FA becomes stronger as the carbon number of FA increases, leading to poor wettability by the test medium and consequent delayed release.

It is suggested from the *in vitro* release behaviors shown in Figs. 1 and 2 that FA–NAA formed with FA which have longer alkyl chains may be applicable to the preparation of sustained-release drug products. Regarding the clinical applications of FA–NAA, it is suggested that a sudden increase of the serum concentration of NAA, which brings about the side effects, can be suppressed by the administration of FA–NAA instead of NAA. FA–NAA is expected as a new drug product under the present situation that a sustained-release dosage of nicotinic acid derivatives is in the process of development.

Conclusion

The rate of release of NAA from FA–NAA decreased regularly with increasing n in only even-numbered or odd-numbered FA. The values of T_{50} or T_{80} for FA–NAA formed with odd-numbered FA was larger than that for FA–NAA formed with even-numbered FA whose alkyl chain length is one more carbon number longer.

It is concluded that FA–NAA as a sustained-release drug product could be clinically useful, through the investigation of the optimum dosage form of FA–NAA and extensive preliminary examinations in experimental animals and eventually human volunteers will be required.

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