

Hygroscopicities of 3-Aminopyridine (3AP) and Fatty Acid Complexes (FA-3AP), and the Release of 3AP from FA-3AP

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The hygroscopicity of 3-aminopyridine (3AP) and fatty acids complexes (FA-3AP) was measured under various levels of humidity at 30°C, where the carbon number (*n*) of the constituent fatty acid (FA) was 14—18. The release behavior of 3AP from FA-3AP was then examined in a JP XII dissolution test apparatus using JP XII disintegration test medium No. 1 (pH 1.2) at 37°C.

3AP was extremely hygroscopic: 3AP was completely deliquesced during storage at relative humidity levels above 80%. In contrast, FA-3AP did not absorb moisture even at 100% relative humidity during at least one month of storage.

3AP was released speedily from FA-3AP in the aqueous test medium. The values of T_{50} and T_{80} , which represent the time required for 50% and 80% of 3AP to release, were 1—3 and 2—6 min, respectively for five different types of FA-3AP. The values of T_{50} or T_{80} for FA-3AP formed with odd-numbered FA were larger than those for FA-3AP formed with even-numbered FA, which has an alkyl chain length one carbon number longer, though the values of T_{50} or T_{80} increased rather regularly with an increase in alkyl chain length for only even-numbered or odd-numbered FA. This was the same tendency as previously observed for the FA-nicotinamide complex.

Keywords 3-aminopyridine; hygroscopicity; complex; fatty acid; release

3-Aminopyridine (3AP), which is used in the manufacture of drugs and dyes, has the disadvantages of hygroscopicity and an amine odor. We have found¹⁾ that 3AP forms a crystalline complex with fatty acid (FA) in a molar ratio of FA to 3AP of 1 : 1, FA-3AP. Such a crystalline complex formed with FA and a water-soluble drug has been found for thiamine disulfide (TDS), (FA)₆ (TDS), and nicotinamide (NAA), FA-NAA, and the release behavior of TDS²⁾ or NAA³⁾ from the complex has also been examined. In previous studies, it has been found that the bitter taste and the hygroscopicity of TDS can be overcome by complexation with FA, and that a FA complex with TDS or NAA is applicable to the preparation of a sustained-release drug formulation. Furthermore, it has been suggested that FA-NAA is clinically useful from the viewpoint of having minimal side effects.

The basic physicochemical properties of FA-3AP have already been studied by elemental analysis, differential scanning calorimetry and Fourier transform infrared (FT-IR) spectroscopy.¹⁾ From that study,¹⁾ it was suggested that FA-3AP has a structure similar to (FA)₆ (TDS) and FA-NAA. The only difference in FA-3AP from the other two FA complexes is the melting point: the melting point of FA-3AP is lower than that of the constituent FA, while the melting points of (FA)₆ (TDS) and FA-NAA are higher than that of the constituent FA. Namely, it is suggested that the binding force between FA and 3AP is weaker than that between FA and (TDS or NAA). It would, therefore, be interesting to know whether the pharmaceutical applications as observed for (FA)₆ (TDS) and FA-NAA could be expected for FA-3AP.

FA-3AP has the advantage of lacking an amine odor. In addition, the FA-3AP used here was not waxlike or fishlike in odor, although FA-3AP formed with unsaturated FA (for example, icosapentaenoic acid) may have a fishlike odor. Further usefulness of FA-3AP in pharmaceuticals will be investigated. This paper presents the results of a comparison of hygroscopicity between 3AP and FA-3AP and a release study of 3AP from FA-3AP.

Experimental

Materials 3AP, tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17) and octadecanoic acid (C18) were the same as those used previously.¹⁾ FA-3AP were prepared as previously described.¹⁾ The purity of FA-3AP was examined with a melting point-measuring apparatus equipped with a microscope ($\times 100$), and it was confirmed that no extra free FA and/or 3AP was present. Crystals of FA-3AP were passed through 48, 60, 100 and 140 mesh sieves, and the particles of 48—60 and 100—140 mesh were collected.

Measurement of Hygroscopicity Portions of about 1g of 3AP and FA-3AP (100—140 mesh) were preserved in desiccators containing aqueous saturated solutions of various salts (KCl, NH₄H₂PO₄, and H₂O), giving relative humidity values of 80, 90 or 100%. The desiccators were kept at constant temperature (30°C). The samples were weighed at appropriate time intervals during storage. This measurement of hygroscopicity is the same as that described in a paper⁴⁾ by Yamamoto.

Measurement of Release Rate The release of 3AP from FA-3AP was tested in a JP XII dissolution test apparatus (paddle method) in 500 ml of JP XII disintegration test medium No. 1 (pH 1.2) at an agitation speed of 200 rpm at 37°C. The effect of particle size on the release rate has been investigated,²⁾ and the particle size of 48—60 mesh is suggested to be suitable at least for a subsequent study. The particle size of FA-3AP in this study was, therefore, set at a limit of 48—60 mesh. About 17—20 mg of each FA-3AP (this corresponds to about 5 mg of 3AP) was used in the test. Aliquots of 5 ml of the sample solution were withdrawn at appropriate time intervals, and the volume was kept constant by replacement with 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 3AP is released. All release experiments were carried out in at least triplicate, and the results were highly reproducible. The release rates are shown as the time required for 50% or 80% of 3AP to be released (T_{50} or T_{80}).

Quantitative Analysis of 3AP The concentration of 3AP was determined spectrophotometrically at a wavelength of 247 nm. The relationship between concentration and absorbance was found to obey Beer's law, and the molar absorptivity (ϵ_{247}) was obtained as 7.345×10^3 mol⁻¹ dm³ cm⁻¹.

Solubility of 3AP 3AP dissolved immediately in the acidic test medium. It is considered that the dissolution rate of 3AP is negligible in determining the release rate of 3AP from FA-3AP.

Results and Discussion

Hygroscopicity The data involving the hygroscopicity of 3AP and five kinds of FA-3AP (C14-3AP, C15-3AP, C16-3AP, C17-3AP, C18-3AP) during storage under

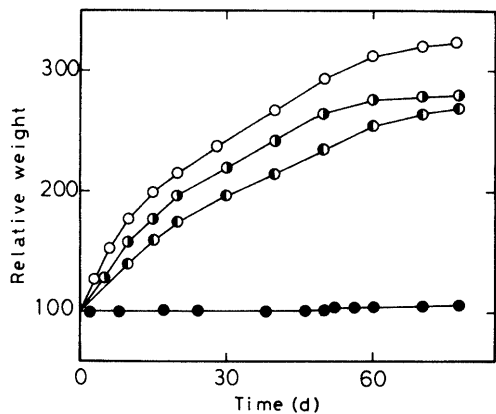


Fig. 1. Comparison of Hygroscopicity between 3AP and FA-3AP
 Relative humidity: ○, 100%; ◐, 90%; ◑, 80% (for 3AP). ●, 100% (for five kinds of FA-3AP). Temperature: 30 °C. Particle size: 100–140 mesh.

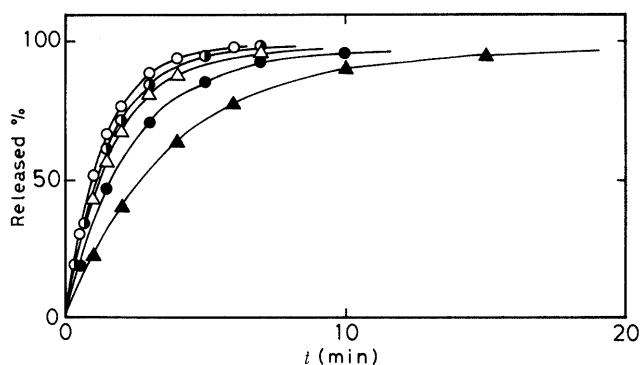


Fig. 2. Release Behavior of 3AP from FA-3AP with Varying Alkyl Chain Lengths
 Carbon numbers in FA: ○, 14; ◐, 16; ●, 18; △, 15; ▲, 17. Particle size: 48–60 mesh. Temperature: 37 °C.

various levels of humidity are shown in Fig. 1. The sample of 3AP alone absorbed moisture rapidly at relative humidity levels of at least 80%, and about 1 g of sample was completely deliquesced. Afterward, the sample of 3AP underwent an oxidizing reaction, the relative weight of the sample increased gradually, and the deliquesced colorless solution was tinged with brown. In contrast, the five kinds of FA-3AP did not absorb moisture, even at 100% relative humidity, during 45 d storage, although an extremely small increase in weight was observed during storage beyond 50 d. As a result, the remarkable hygroscopicity of 3AP, which is completely deliquesced by moisture, was overcome dramatically by complexation with FA. This property of the FA complex with regard to improving hygroscopicity is very useful for other hygroscopic compounds.

Release Behavior of 3AP from FA-3AP The release behavior of 3AP from FA-3AP was examined, and the results are shown in Fig. 2. The percentage of released 3AP was calculated with respect to the total concentration of 3AP theoretically contained in the 1:1 complex, FA-3AP. As can be seen in Fig. 2, 3AP was released about 96–98% from FA-3AP.

The values of T_{50} and T_{80} are plotted against n in Fig. 3. To indicate the variation in measured values, the difference between minimum and maximum values is shown by a bar in Fig. 3. Where no bar is shown, the value lies

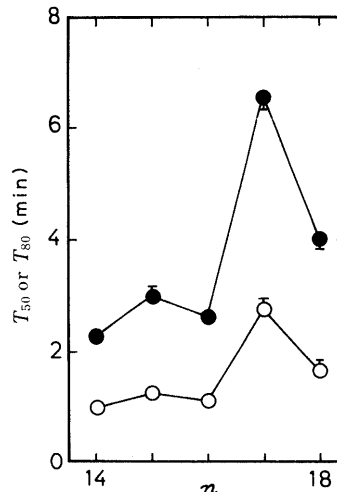


Fig. 3. Effect of FA on the Release Time (T_{50} or T_{80}) of 3AP from FA-3AP

Time required for 50% or 80% of 3AP to release: ○, T_{50} ; ●, T_{80} . Particle size: 48–60 mesh. Temperature: 37 °C.

within the symbol. As is evident from the values of T_{50} and T_{80} , the release of 3AP from FA-3AP is speedy. Campagna *et al.*⁵⁾ showed a close relationship between the release time of a drug and its therapeutic efficacy. So, the release behavior observed for FA-3AP suggests that its therapeutic efficacy should be sufficiently ensured when the FA complex is administered.

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 tendency is similar to that observed for the release of NAA from FA-NAA³⁾ and TDS from (FA)₆ (TDS).²⁾ A similar release pattern with regard to the (T_{50} or T_{80}) vs. n plots was found among FA-3AP, FA-NAA and (FA)₆ (TDS), although the melting point behavior of FA-3AP is different from FA-NAA and (FA)₆ (TDS): the melting point of FA-3AP is lower than that of the original FA,¹⁾ while the melting points of FA-NAA and (FA)₆ (TDS) are higher than that of the original FA. The delayed release rate for FA-3AP composed of odd-numbered FA may be due to the fact that the interaction between odd-numbered FA and 3AP is stronger than that between even-numbered FA and 3AP. This is also reflected in the melting points of FA-3AP: the melting points of FA-3AP formed with even-numbered FA are about 10–13 °C lower than those of the original even-numbered FA, while the melting points of FA-3AP formed with odd-numbered FA are about 7–8 °C lower than those of the original odd-numbered FA. Namely, the thermostability of odd-numbered FA is maintained to a greater extent than that of even-numbered FA when FA-3AP is formed.

(FA)₆ (TDS) and FA-NAA indicated a sustained-release behavior,^{2,3)} whereas FA-3AP did not indicate a sustained-release behavior. It is suggested that FA complexes whose melting points are higher than those of the original FA may indicate a sustained-release behavior and that FA complexes whose melting points are lower than those of the original FA may indicate a speedy-release behavior.

The amine odor and the deliquescence of 3AP were

completely overcome by complexation with FA. Furthermore, 3AP was released speedily in a pH 1.2 aqueous medium. The characteristics of a FA complex such as FA-3AP may be useful for drugs which have an amine odor and/or deliquescence, though 3AP is not independently used as a drug.

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