Hygroscopicity and Dissolution of Thiamine Disulfide–Higher Fatty Acids Complexes

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The hygroscopicity of the complexes composed of thiamine disulfide (TDS) and higher fatty acids and the dissolution of TDS from the complexes were studied. The hygroscopicity of TDS was reduced dramatically by the formation of the (fatty acid)$_6$(TDS) complexes. Regarding the dissolution of TDS from the complexes, plots of T_{50} or T_{80} (the time required for 50% or 80% of TDS to dissolve, respectively) against the carbon numbers of the constituent fatty acids showed a zig-zag pattern, and C17 fatty acid gave the longest T_{50} and T_{80}.

Keywords thiamine disulfide; complex; higher fatty acid; dissolution; hygroscopicity; particle size

Thiamine disulfide (TDS), which is a derivative of vitamin B_1, has the disadvantages of hygroscopicity and a bitter taste. We have prepared the (fatty acid)$_6$(TDS) complexes with the aim of overcoming these defects. The physicochemical properties of the complexes have already been reported.[1] The (fatty acid)$_6$ (TDS) complexes do not have a bitter taste and are expected to be useful as drug products.

When the (fatty acid)$_6$(TDS) complexes are administered orally, TDS dissolves from the complexes, and a detailed knowledge of the dissolution characteristics of TDS from the complexes is required for pharmaceutical applications. This paper presents the results of a dissolution study and a comparison of hygroscopicity between TDS and (fatty acid)$_6$(TDS) complexes.

Experimental

Materials TDS, tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17), and octadecanoic acid (C18) were the same as those used previously.[1] Complexes composed of TDS and higher fatty acids were prepared as previously described.[1] Purities of complexes were examined with a melting point-measuring apparatus equipped with a microscope (× 100), and it was confirmed that no extra free fatty acid and/or TDS was present. Crystals of complexes were passed through 20, 32, 48, 60, 100, and 140 mesh sieves, and the particles of 20—32, 48—60, and 100—140 mesh were collected.

Measurement of Moisture Absorption Portions of about 1 g of various samples (100—140 mesh) were preserved in desiccators containing aqueous saturated solutions of various salts (KCl, $NH_4H_2PO_4$, and H_2O), giving relative humidity values of 80, 90, or 100%. The desiccators were kept at a constant temperature (40 °C). The samples were weighed at appropriate time intervals during storage. This measurement of moisture absorption is the same as that described in a paper[2] by Yamamoto.

Measurement of Dissolution Dissolution of TDS from complexes was tested in a JP XI dissolution test apparatus (paddle method) in 500 ml[3] of JP XI disintegration test medium No. 1 (pH 1.2) at an agitation speed of 200 rpm at 37 °C. About 30 mg of TDS–fatty acids complexes (this corresponds to 7—8 mg of TDS) 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 dissolution medium at the same temperature. The sample solution was filtered immediately through a glass filter (G-3), and the absorbance was determined. All dissolution experiments were carried out at least in triplicate and the results were highly reproducible. The dissolution rates are shown as the times required for 50% or 80% of TDS to dissolve (T_{50} or T_{80}).

Quantitative Analysis of TDS The concentration of TDS was determined spectrophotometrically at a wavelength of 242 nm. The relationship between concentration and absorbance was found to obey Beer's law, and the molar absorptivity (ε_{242}) was obtained as 2.607×10^4 $mol^{-1}\,dm^3$.

Results and Discussion

Moisture Absorption The moisture absorption data for TDS and five kinds of complexes (C14–TDS, C15–TDS, C16–TDS, C17–TDS, C18–TDS) during storage under various levels of humidity are shown in Fig. 1. TDS was found to absorb moisture at relative humidity levels of above 80%. In contrast, the five kinds of complexes did not absorb moisture even at 100% relative humidity. The hygroscopicity of TDS is, therefore, greatly reduced by the formation of complexes with higher fatty acids.

Effect of Fatty Acids and Particle Size The effect of the fatty acids which are components of the complexes on the dissolution behavior of TDS from the complexes was examined under the condition that the particle size of crystals of complexes was constant (48—60 mesh), and the

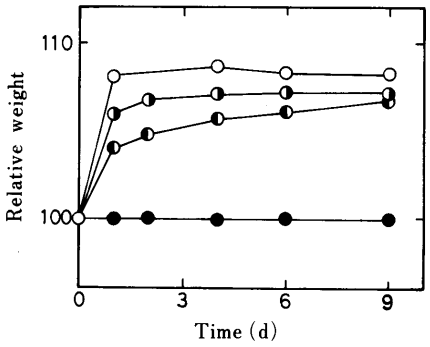

Fig. 1. Comparison of Hygroscopicity between TDS and TDS–Fatty Acids Complexes

Relative humidity: ○, 100%; ◑, 90%; ◐, 80% (for TDS). ●, 100% (for five kinds of complexes). Temperature: 40 °C. Particle size: 100—140 mesh.

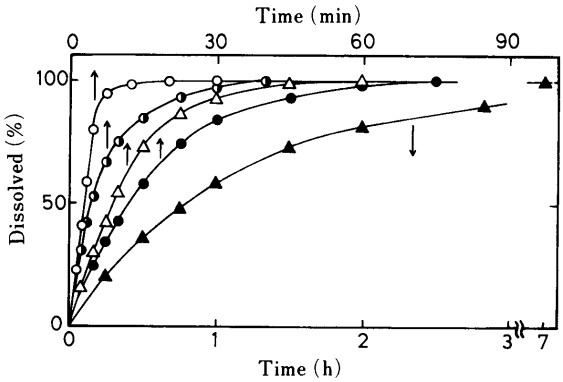

Fig. 2. Effect of Fatty Acids on Dissolution Behavior of TDS from TDS–Fatty Acids Complexes

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

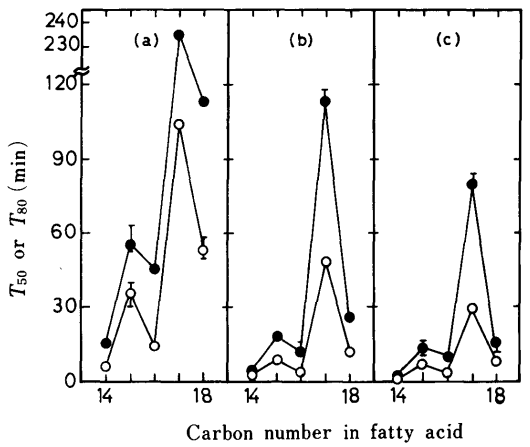

Fig. 3. Effect of Fatty Acids and Particle Size on Dissolution Rate (T_{50} or T_{80}) of TDS from TDS–Fatty Acids Complexes

Particle size: (a), 20—32 mesh; (b), 48—60 mesh; (c), 100—140 mesh. Time required for 50% or 80% of TDS to dissolve: ○, T_{50}; ●, T_{80}. Temperature: 37 °C.

results are shown in Fig. 2. The percentages of dissolved TDS were calculated with respect to the total concentration of TDS which is theoretically contained in the complex whose composition is expressed stoichiometrically by the formula (fatty acid)$_6$ (TDS). As can be seen in Fig. 2, TDS was dissolved to the extent of about 100% from the complexes in all cases.

The values of T_{50} and T_{80} (the times required for 50% and 80% of TDS to dissolve) are plotted against the carbon numbers of the alkyl chain of fatty acids in Fig. 3. To indicate the variation in measured values, the difference between minimum and maximum values is shown by a bar (I) in Fig. 3. Where no bar is shown, it lies within the symbol. The values of T_{50} and T_{80} were found to increase with increasing particle size. A similar tendency has been reported for phenytoin.[3]

The relationship between the carbon number of fatty acid and dissolution time (T_{50} or T_{80}) was a zig-zag one, though the values of T_{50} or T_{80} increased rather regularly with increase of the alkyl chain length for only even-numbered or odd-numbered fatty acids. The delayed dissolution rate for the complexes composed of odd-numbered fatty acids may be considered to be due to greater stability of the odd-numbered fatty acids–TDS complexes as compared with the even-numbered fatty acids–TDS complexes. This is also reflected in the melting points of the complexes: the melting points of the complexes formed from even-numbered fatty acids are about 10 °C higher than those of the original even-numbered fatty acids,[1] while the melting points of the complexes formed from odd-numbered fatty acids are about 15 °C higher than those of the original odd-numbered fatty acids.[1] Furthermore, the powder X-ray diffraction patterns of the complexes suggest that the crystal structures of complexes with odd-numbered fatty acids are a little different from those with even-numbered fatty acids. Namely, it is suggested that the interaction between odd-numbered fatty acids and TDS might be stronger than that between even-numbered fatty acids and TDS. The significance of the difference in the powder X-ray diffraction patterns of complexes is being further investigated. Furthermore, we are now studying calorimetrically the heat of dissolution, and investigating the energy of formation of the complexes (number of hydrogen bonds between TDS and fatty acids). The results will be reported in due course.

Regarding the relationship between T_{50} and bioavailability, a high correlation between the reciprocal of T_{50} and the maximum drug concentration in the blood or the urinary excretion rate of drug has been reported for sugar-coated tablets of TDS.[4] Furthermore, many related studies[5] have been reported since Campagna *et al.*[6] showed a close relationship between the dissolution of a drug and its therapeutic efficacy.

We consider that the TDS–fatty acids complexes could be clinically useful for oral administration, though extensive preliminary examinations in experimental animals and eventually human volunteers will be required. Furthermore, the optimum dosage form of the complexes will need to be investigated.

The effect of higher fatty acids which are components of the complexes on the dissolution rate of TDS will be reported in detail in a subsequent paper from the viewpoint of thermodynamics.

Conclusion

The dissolution behavior of TDS from TDS–fatty acids complexes was determined. Plots of the times required for 50% or 80% of TDS to dissolve (T_{50} or T_{80}) against the carbon numbers of fatty acids which are components of the complexes showed a zig-zag line; odd-carbon-numbered fatty acids gave more stable complexes.

TDS–fatty acids complexes may be clinically useful for oral administration. Furthermore, the characteristic of the complexes formed with fatty acids might be applicable to the preparation of a sustained-release drug formulation.

References

1) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, and A. Kaneko, *Bitamin*, **61**, 57 (1987).
2) R. Yamamoto, *Yakuzaigaku*, **18**, 245 (1958).
3) S. Yakou, S. Yamazaki, T. Sonobe, M. Sugihara, K. Fukumuro, and T. Nagai, *Chem. Pharm. Bull.*, **34**, 4400 (1986).
4) N. Aoyagi, H. Ogata, N. Kaniwa, M. Koibuchi, T. Shibazaki, A. Ejima, M. Mizobe, K. Kohno, and M. Samejima, *Chem. Pharm. Bull.*, **34**, 281 (1986); *idem*, *ibid.*, **34**, 292 (1986).
5) A. J. Aguiar, L. M. Wheeler, S. Fusari, and J. E. Zelmer, *J. Pharm. Sci.*, **57**, 1844 (1968); E. J. Fraser, R. H. Leach, and J. W. Poston, *Lancet*, II, **1972**, 541.
6) F. A. Campagna, G. Cureton, R. A. Mirigian, and E. Nelson, *J. Pharm. Sci.*, **52**, 605 (1963).