Thermodynamic Study on Release of Thiamine Disulfide (TDS) from TDS-Higher Fatty Acids Complexes. I. Effect of Even-Numbered Fatty Acids

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The rates of release of thiamine disulfide (TDS) from higher fatty acid–TDS complexes were determined in a JP XI dissolution test apparatus in JP XI disintegration test medium No. 1 (pH 1.2) at various temperatures, and the thermodynamic quantities for the release of TDS from the complexes were estimated. The concentration of TDS was determined spectrophotometrically.

The rate of release of TDS from the complexes decreased with increasing carbon number in the fatty acid and increased at higher temperature. The values of free energy change ΔG, entropy change ΔS, and enthalpy change ΔH for the release of TDS from the complexes were all positive. The release of TDS from the complex was found to be an enthalpically controlled reaction.

The release of TDS from octadecanoic acid–TDS complex, $(SA)_6(TDS)$, was found to be most disadvantageous from the enthalpic viewpoint and most advantageous from the entropic viewpoint as compared with the complexes formed with hexadecanoic acid and tetradecanoic acid. Furthermore, the largest value of activation energy for the release of TDS from $(SA)_6(TDS)$ was found to correspond to the largest positive value of free energy change for the release of TDS.

Keywords thiamine disulfide; complex; higher fatty acid; release; sustained release; thermodynamics; activation energy; free energy change; enthalpy change; entropy change

From the pharmaceutical point of view, thiamine disulfide (TDS), which is a derivative of vitamin B_1, has the disadvantages of hygroscopicity and bitter taste. We have prepared higher fatty acids (FA)–TDS complexes in an attempt to overcome these problems. The stoichiometry of the complexes can be expressed as $(FA)_6(TDS)$.[1] These complexes are neither bitter nor hygroscopic.[2] The possibility of application of the complexes in the pharmaceutical field has already been discussed in a previous paper.[2] In a study of the dissolution of TDS from the complexes, very interesting results were obtained as the length of the alkyl chain of the fatty acid was changed; namely (1) the plots of T_{50} or T_{80} which are the times required for 50% or 80% of TDS to dissolve, showed a zigzag line owing to the difference between even- and odd-carbon-numbered fatty acids, (2) the values of T_{50} or T_{80} increase with an increase of the alkyl chain length in even- or odd-numbered fatty acids.[2]

The effect of particle size on the dissolution rate has been found to decrease with increasing particle size.[2,3] The particle size of 48—60 mesh was suggested to be suitable[2] at least for a subsequent study.

Many studies[4] showing that the dissolution rates of drugs are increased by inclusion complexation with β-cyclodextrin have beeh reported. Additionally, an improvement in the solubility of tioxacin by complexation with aliphatic amines has been reported.[5] On the other hand, several reports[6,7] on sustained drug delivery have been published. For the purpose of preparing sustained-release drug formulations, polylactic acid[6] and chitosan[7] have been used. The FA–TDS complex is quite different from such known[7,8] drug products, and the characteristics of the complexes formed with fatty acids might be applicable to the preparation of a new type of sustained-release drug formulation.

From these points of view, the release rates of TDS from complexes whose particle size was 48—60 mesh were determined at various temperatures to investigate in detail the effect of the fatty acids. Furthermore, the activation energy and changes in enthalpy and entropy for the release of TDS from the complexes were estimated from the release rate constants, and the effects of different fatty acids is discussed from the viewpoint of thermodynamics. The results obtained for even-numbered FA–TDS complexes are presented in this paper.

Experimental

Materials TDS, tetradecanoic acid (MA), hexadecanoic acid (PA), and octadecanoic acid (SA) were the same as those used for the previous studies.[1,2] Complexes composed of TDS and higher fatty acids were prepared as previously described.[1] The purity of each complex was examined as described in the previous paper.[2] Crystals of complexes were passed through 48 and 60 mesh sieves, and the particles of 48—60 mesh were taken for dissolution test.

Measurement of Release of TDS from Complexes The release of TDS from the complexes was determined in a JP XI dissolution test apparatus (paddle method) in JP XI disintegration test medium No. 1 (pH 1.2) as described in the previous paper.[2] Experiments were carried out not only at 37 °C[2] but also at 17, 27, and 47 °C. All experiments were carried out in triplicate and the results were highly reproducible.

Quantitative Analysis of TDS The concentration of TDS was determined spectrophotometrically as previously described.[2] The molar absorptivity (ε_{242}) of anhydrous TDS is 2.607×10^4 mol^{-1} dm^3.[2] TDS recovered from the complexes was found to be anhydrous[1] although TDS used for the preparation of complexes was a hydrate.

Solubility of TDS TDS dissolved immediately in the test medium (pH 1.2).[2,8] The dissolution rate of TDS is, therefore, considered not to be rate-determining in the release of TDS from the complexes (dissolution rate ≫ release rate; time required for the release of TDS from the complex ≫ time required for the dissolution of TDS).

Results

Release Behavior of TDS from $(FA)_6(TDS)$ The release behavior of TDS from $(SA)_6(TDS)$, $(PA)_6(TDS)$, and $(MA)_6(TDS)$ at four temperatures is shown as a relationship between the percentage of released TDS and time in Figs. 1—3, respectively. The percentages of released TDS were calculated with respect to the theoretical total con-

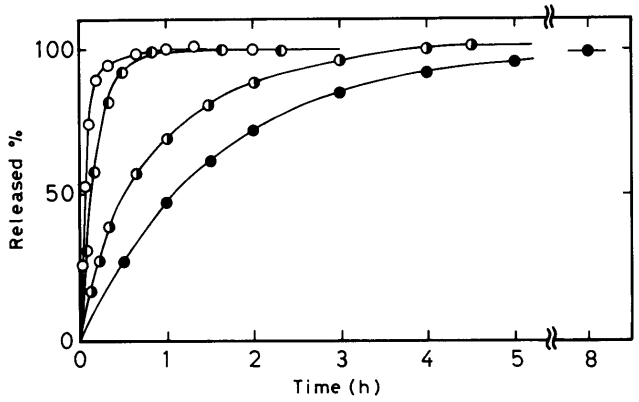

Fig. 1. Effect of Temperature on Release Behavior of TDS from $(SA)_6$(TDS)

Temperature: ●, 17 °C; ◑, 27 °C; ◐, 37 °C; ○, 47 °C. Particle size: 48—60 mesh.

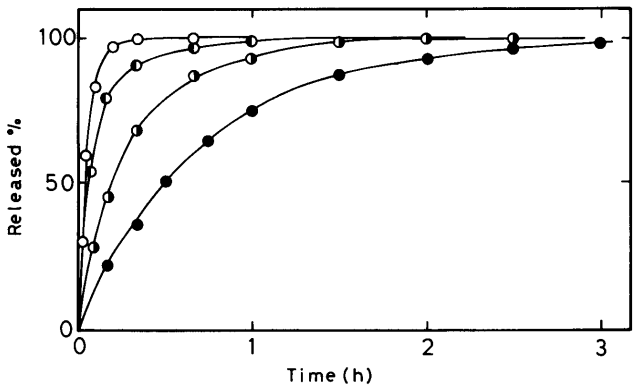

Fig. 2. Effect of Temperature on Release Behavior of TDS from $(PA)_6$(TDS)

Symbols are the same as in Fig. 1.

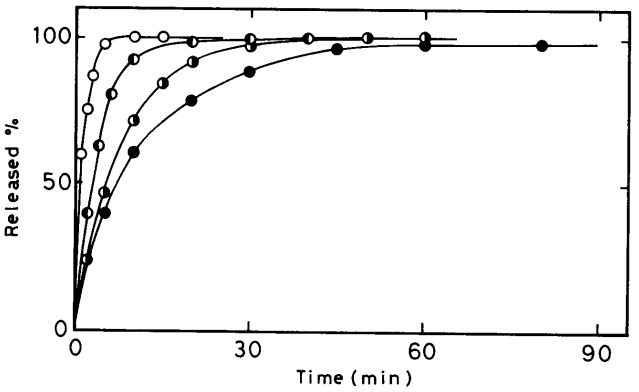

Fig. 3. Effect of Temperature on Release Behavior of TDS from $(MA)_6$(TDS)

Symbols are the same as in Fig. 1.

centration of TDS which is contained in the complex whose composition is expressed stoichiometrically by the formula $(FA)_6$(TDS). As can be seen in Figs. 1—3, TDS was released to the extent of about 100% from the complexes in all cases. Furthermore, the release rate is faster under the conditions of higher temperature and shorter alkyl chain of the fatty acid.

Rate Constant for Release of TDS from $(FA)_6$(TDS) The rate constant for the release of TDS (Figs. 1—3) is defined as follows:

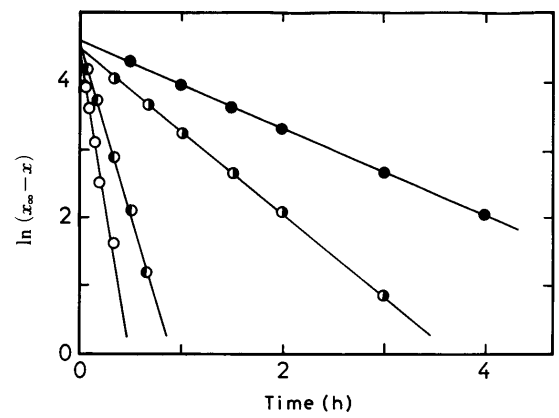

Fig. 4. Effect of Temperature on Release of TDS from $(SA)_6$(TDS), $\ln(x_\infty - x)$ *vs.* Time

Symbols are the same as in Fig. 1.

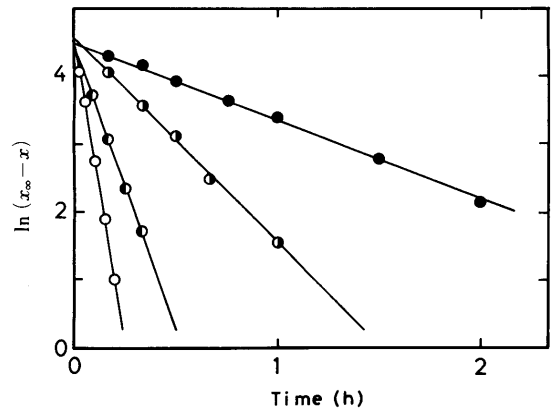

Fig. 5. Effect of Temperature on Release of TDS from $(PA)_6$(TDS), $\ln(x_\infty - x)$ *vs.* Time

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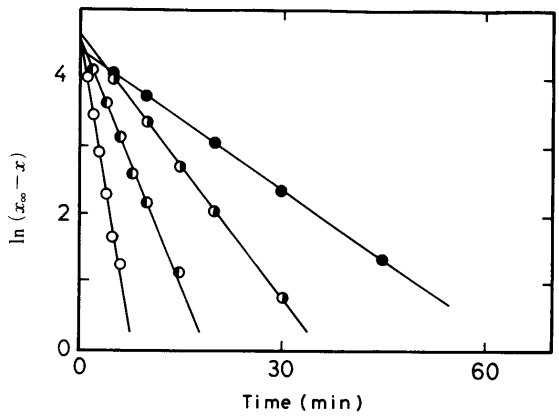

Fig. 6. Effect of Temperature on Release of TDS from $(MA)_6$(TDS), $\ln(x_\infty - x)$ *vs.* Time

Symbols are the same as in Fig. 1.

$$\ln(x_\infty - x) = \ln x_\infty - kt \quad (1)$$

where k is the rate constant of release, x is the percentage of TDS released from the complexes during time t, and x_∞ is the final value of released TDS at time ∞. The values of x_∞ are approximately 100 (98.8—101.3), as can be seen in Figs. 1—3. Plots of $\ln(x_\infty - x)$ *versus* t, calculated from the values shown in Figs. 1—3, are presented in Figs. 4—6. As can be

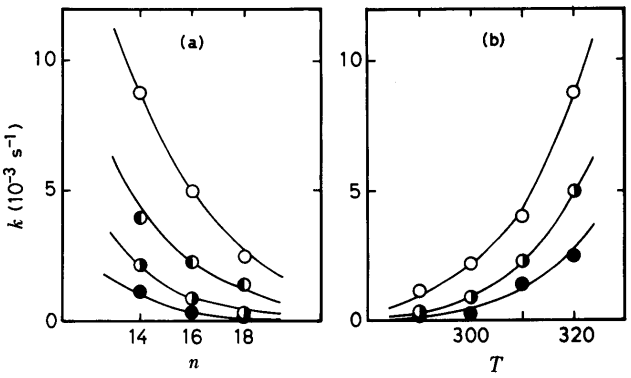

Fig. 7. Relationship among Rate Constant for Release of TDS (k), Carbon Number in FA (n), and Temperature (T)

(a) Plots of k *vs.* n. Temperature: ●, 17 °C; ◑, 27 °C; ◐, 37 °C; ○, 47 °C.
(b) Plots of k *vs.* T. Carbon numbers in FA: ○, 14; ◑, 16; ●, 18.

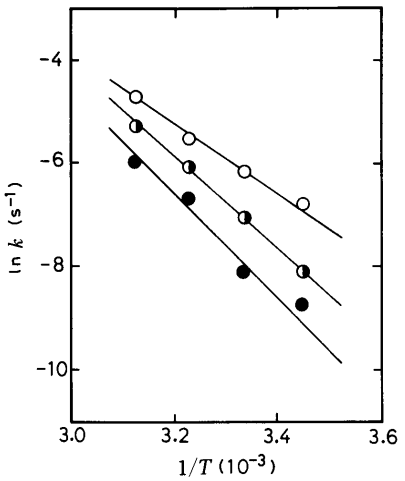

Fig. 8. Arrhenius Plots

Carbon numbers in FA: ○, 14; ◑, 16; ●, 18.

seen in Figs. 4—6, good linear relationships were obtained in all cases. The release rate is, therefore, found to be first-order. The values of release rate constant k were obtained from the slopes shown in Figs. 4—6, and the relationships between k and carbon numbers in FA and between k and temperature are shown in Fig. 7. The value of k decreased with increasing carbon number in FA, and increased exponentially with increasing temperature.

Discussion

Activation Energy for Release of TDS from $(FA)_6$(TDS) As can be seen in Fig. 7b, the rate constant for the release of TDS from complexes, k, was found to depend on temperature. The activation energy for the release can, therefore, be calculated from the values of k. According to the theory of Arrhenius, the relationship between release rate constant and temperature is represented as follows:

$$\ln k = -\frac{\Delta E}{R} \cdot \frac{1}{T} + \ln A \qquad (2)$$

where ΔE is the activation energy for the release, R is the gas constant (8.314 J deg^{-1} mol^{-1}), T is the absolute temperature, and A is a constant which is called the frequency factor. Plots of $\ln k$ *versus* $1/T$ based on Eq. 2 are shown in Fig. 8. As is clear in Fig. 8, the relationship between $\ln k$ and $1/T$ can be represented by a single line which depends on the alkyl chain length of FA. The activation energy for the release was, therefore, obtained from the value of the slope, and the results are summarized in Table I. As can be seen in Table I, the value of activation energy for the release of TDS from $(SA)_6$(TDS) is largest, and the value of activation energy decreases with decreasing carbon number of FA. The delayed release of TDS from $(SA)_6$(TDS) is caused by the large value of activation energy.

The crystal structure of $(FA)_6$(TDS) has not yet been determined. The relationship between the activation energy and the carbon number of FA, therefore, can not be discussed in detail. However, it is considered that one factor is 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 dissolution medium and consequent delayed release.

Regarding the complexes composed of higher fatty acids and urea, it has been reported that the stability of the complex increases with the chain length of the fatty acid.[9] This phenomenon is similar to our findings.

Table I. Thermodynamic Quantities for Release of TDS from $(FA)_6$(TDS)

	ΔE (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1})
$(SA)_6$(TDS)	84.9	83.8	213
$(PA)_6$(TDS)	74.0	71.7	180
$(MA)_6$(TDS)	57.3	55.4	134

It has been suggested from the infrared (IR) spectrum of $(FA)_6$(TDS)[1] that hydrogen bonding contributes to the formation of the complexes. The release rate of TDS from the complexes may, therefore, be affected by the number of hydrogen bonds between TDS and FA. Further studies are necessary. We are now studying calorimetrically the heat of dissolution for $(FA)_6$(TDS), TDS, and FA.

Regarding the activation energy for the release of the compound from the complex, studies on the deamination of theophylline–aliphatic amine complexes by thermal analysis have been reported.[10] According to the results, the values of activation energy are about 45—60 kJ mol^{-1} for monoalkyl amines,[10a] 60—70 kJ mol^{-1} for alkanol amines,[10a] and 60—95 kJ mol^{-1} for alkyl diamines.[10b] The values of activation energy for the release of TDS from $(FA)_6$(TDS) are similar to the values[10] for theophylline–aliphatic amine complexes, suggesting a similar binding energy between TDS–FA complexes and theophylline–aliphatic amines complexes.

Thermodynamic Quantities for Release of TDS from $(FA)_6$(TDS) The change of free energy, ΔG, for the release of TDS from $(FA)_6$(TDS) can be represented in terms of the release rate constant, k, as follows:

$$\Delta G = -RT\ln k \qquad (3)$$

The values of ΔG were estimated from the values of k shown in Fig. 7, and the results are presented in Fig. 9 as a relationship between free energy change and carbon number of FA. All values of ΔG are positive, indicating that the system becomes unstable with the release of TDS from $(FA)_6$(TDS) and that the release reaction does not proceed spontaneously. Furthermore, the positive value of ΔG

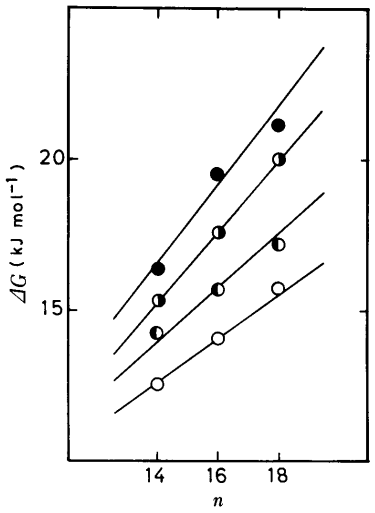

Fig. 9. Free Energy Changes (ΔG) for Release of TDS from $(FA)_6$(TDS)
Temperature: ●, 17 °C; ◑, 27 °C; ◐, 37 °C; ○, 47 °C.

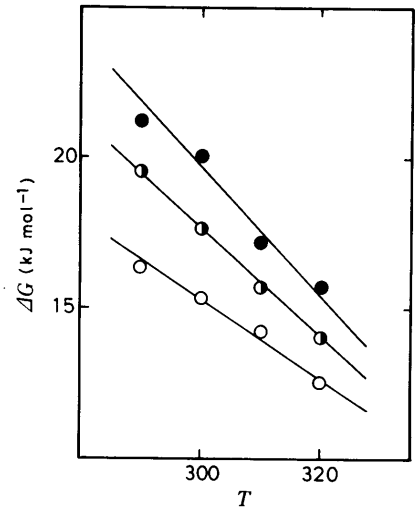

Fig. 10. Relationship between Free Energy Changes and Temperature
Symbols are the same as in Fig. 8.

becomes larger as the carbon number of FA increases, indicating that the release of TDS is more difficult from $(FA)_6$(TDS) formed with FA which has a longer alkyl chain.

We investigated whether enthalpy change or entropy change contributes to the positive value of free energy change. Free energy change ΔG is related to enthalpy change ΔH and entropy change ΔS as follows:

$$\Delta G = \Delta H - T\Delta S \quad (4)$$

According to Eq. 4, the values of ΔG were plotted against the absolute temperature T, and the relationship is shown in Fig. 10. As can be seen in Fig. 10, the relationship between ΔG and T can be represented by a single line which depends on the alkyl chain length of FA. The entropy change ΔS and the enthalpy change ΔH were, therefore, obtained from the values of the slope and intercept, and the results are summarized in Table I. As can be seen in Table I, the values of ΔH and ΔS are positive. This indicates that the release of TDS from $(FA)_6$(TDS) is advantageous entropically but disadvantageous enthalpically. Furthermore, the enthalpic disadvantage is greater than the entropic advantage ($\Delta H > T\Delta S$), leading to a positive value of ΔG. The release of TDS from $(FA)_6$(TDS) is, therefore, an enthalpically controlled reaction. Furthermore, the positive value of ΔH shows that the release of TDS is an endothermic reaction, indicating that the release reaction proceeds more easily at higher temperature from the enthalpic viewpoint. Next, a comparison among the values of thermodynamic quantities for $(SA)_6$(TDS), $(PA)_6$(TDS), and $(MA)_6$(TDS) was made. The positive value of ΔH for $(SA)_6$(TDS) is largest, and the value of ΔH becomes smaller as the alkyl chain of FA becomes shorter. This indicates that the release of TDS from $(SA)_6$(TDS) is most disadvantageous from the enthalpic viewpoint. On the other hand, the positive value of ΔS for $(SA)_6$(TDS) is largest, and the value of ΔS becomes smaller as the alkyl chain of FA becomes shorter. This indicates that the release of TDS from $(SA)_6$(TDS) is most advantageous from the entropic viewpoint. The release of TDS from $(SA)_6$(TDS) is most disadvantageous from the free energetic viewpoint because the release of TDS from $(FA)_6$(TDS) is enthalpically controlled ($\Delta H > T\Delta S$). The largest value of activation energy for the release of TDS from $(SA)_6$(TDS) is consistent with the fact that $(SA)_6$(TDS) is most thermodynamically stable as compared with the other two complexes, $(PA)_6$(TDS) and $(MA)_6$(TDS).

The differences among the release rates of TDS from the complexes, $(SA)_6$(TDS), $(PA)_6$(TDS), and $(MA)_6$(TDS), can be explained by the thermodynamic parameters.

Conclusion

The rates of release of TDS from the complexes, $(SA)_6$(TDS), $(PA)_6$(TDS), and $(MA)_6$(TDS), were determined and investigated from the viewpoint of thermodynamics.

The rate of release of TDS from the complexes decreased with increasing carbon number in the fatty acid and increased with increasing temperature. The release of TDS from the complex was found to be an enthalpically controlled reaction from the thermodynamic analysis. The release of TDS from $(SA)_6$(TDS) was found to be most disadvantageous from the enthalpic viewpoint and most advantageous from the entropic viewpoint as compared with the other two complexes, $(PA)_6$(TDS) and $(MA)_6$(TDS). Furthermore, the largest value of activation energy for the release of TDS from $(SA)_6$(TDS) was found to be caused by the largest positive value of free energy change for the release of TDS.

From these results, we suggest that: (1) the TDS-complexes formed with fatty acids which have longer alkyl chains could be useful for the preparation of sustained-release drug products because of their thermodynamic stability, (2) it might be possible to control the effective period of drug release by choice of a fatty acid with a proper alkyl chain.

The cost of even-numbered fatty acids is low, and the characteristics of the complexes formed with fatty acids might be applicable (*e.g.* in pain clinics) to the preparation of a sustained-release drug formulation.

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