Temperature Dependence of Bimolecular Reactions Associated with Molecular Mobility in Lyophilized Formulations

Sumie Yoshioka,[1,2] Yukio Aso,[1] and Shigeo Kojima[1]

Received February 21, 2000; accepted May 2, 2000

Purpose. We studied the temperature dependence of acetyl transfer between aspirin and sulfadiazine, a bimolecular reaction, in lyophilized formulations at temperatures near the glass transition temperature (T_g) and NMR relaxation-based critical mobility temperature (T_{mc}), to further understand the effect of molecular mobility on chemical degradation rates in solid pharmaceutical formulations. The temperature dependence of the hydrolysis rates of aspirin and cephalothin in lyophilized formulations was also studied as a model of bimolecular reactions in which water is a reactant.

Methods. Degradation of lyophilized aspirin–sulfadiazine formulations containing dextran and various amounts of water at temperatures ranging from 1°C to 80°C was analyzed by HPLC. The degradation of cephalothin in lyophilized formulations containing dextran and methylcellulose was also analyzed at temperatures ranging from 10°C to 70°C.

Results. Acetyl transfer in lyophilized asprin—sulfadiazine formulations containing dextran exhibited a temperature dependence with a distinct break around T_{mc}, which may be ascribed to a change in the translational mobility of aspirin and sulfadiazine molecules. The hydrolysis of aspirin and cephalothin in lyophilized formulations, which is also a bimolecular reaction, did not show a distinct break, suggesting that water diffusion is not rate-limiting.

Conclusions. The diffusion barrier of water molecules in lyophilized formulations appears to be smaller than the activational barrier of the hydrolysis of aspirin and cephalothin based on the results of this study that the temperature dependence of the hydrolysis rate is almost linear regardless of T_{mc} and T_g. On the other hand, the diffusion barrier of aspirin and sulfadiazine molecules appears to be comparable to the activational barrier of the acetyl transfer reaction between these compounds, resulting in nonlinear temperature dependence.

KEY WORDS: acetyl transfer; hydrolysis; lyophilized formulation; temperature dependence; molecular mobility.

INTRODUCTION

Understanding the temperature dependence of chemical degradation in the solid-state is particularly important in evaluating the feasibility of accelerated stability testing for solid dosage forms. Stability cannot be predicted by extrapolating the degradation rate obtained under accelerated conditions when the temperature dependence changes within a temperature range. Molecular mobility is considered to be one factor that affects the chemical degradation rate of drugs in solid formulations. Since the molecular mobility of amorphous pharmaceuticals exhibits different temperature dependence between temperature ranges below and above their glass transition temperatures (T_g) (1,2), the temperature dependence of the chemical degradation rates in these amorphous systems should also change between these ranges.

The temperature dependence of chemical reactions in the solid-state is generally complicated. The cyclization reaction of amorphous quinapril hydrochloride, which is considered to require a critical amount of translational and/or rotational diffusion, exhibited a temperature dependence with a distinct break near its T_g (3). Several investigators have described the temperature dependence of chemical degradation rates in lyophilized formulations. The hydrolysis rate of aspirin in lyophilized hydroxypropyl-β-cyclodextrin/aspirin complex significantly changes near its T_g (4). On the other hand, the temperature dependence of the hydrolysis rate of peptides in lyophilized formulations containing cross-linked sucrose polymer is not significantly enhanced near T_g (5). The deamidation rate of peptide in lyophilized formulations containing poly(vinylpyrrolidone) increases by barely 2 orders of magnitude around T_g, which was far below the >5 orders expected for the decrease in viscosity around glass transition (6,7). The authors proposed that the level of mobility required for deamidation may be less than that of the matrix mobility. Rather than intramolecular reactions studied in most of these papers, bimolecular reactions may be more seriously affected by the molecular mobility of formulations.

We studied the temperature dependence of acetyl transfer between aspirin and sulfadiazine in lyophilized formulations at a temperature range near T_g, to gain further insight into the effect of molecular mobility on chemical degradation rates in solid pharmaceutical formulations. This reaction can be considered to be a bimolecular reaction in which the translational diffusion of reactant molecules becomes rate-determining when molecular mobility is limited in the solid-state. We also examined the temperature dependence of the hydrolysis rate of cephalothin in lyophilized formulations as a model of bimolecular reactions in which water is a reactant, to explore the possibility that water diffusion becomes rate-limiting. Dextran and methylcellulose (MC) were used as excipients in the lyophilized formulations.

We used the NMR relaxation-based critical mobility temperature (T_{mc})(20 to 30°C lower than the T_g (8)) as a parameter representing molecular mobility in addition to the T_g that is generally considered to reflect matrix mobility. The temperature dependence of the acetyl transfer rates between aspirin and sulfadiazine and the hydrolysis rate of cephalothin was studied at temperatures near T_g and T_{mc}.

MATERIALS AND METHODS

Materials

Sulfadiazine (S-8626), cephalothin (C-4520) and dextran (D-4133, average molecular weight, 42,000) were purchased from Sigma Chemical Co. (St. Louis, MO). Aspirin (015-10262), salicylic acid (199-00142), 4-hydroxybenzoic acid (084-04102) and MC (136-07172, 15cP) were provided by Wako Pure Chemical Industries Ltd. (Osaka). Acetyl sulfadiazine was synthesized from sulfadiazine and acetic anhydride in pyridine.

[1] National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan.

[2] To whom correspondence should be addressed. (e-mail: yoshioka@nihs.go.jp)

0724-8741/00/0800-0925$18.00/0

Table 1. Water Contents of Lyophilized Formulations Containing Dextran and Various Drugs

Relative humidity (%)	Water content (g/g of dry solid)		
	Bovine serum γ-globulin	Cephalothin	Aspirin
12	0.058 ± 0.004	—	0.058 ± 0.004
23.4	0.102 ± 0.005	0.100 ± 0.004	—
60.2	0.178 ± 0.008	0.173 ± 0.009	0.173 ± 0.008
75	0.218 ± 0.008	0.216 ± 0.008	—

Preparation of Lyophilized Formulations

Five grams each of aqueous sulfadiazine solution (0.02 %w/w) and aspirin solution (0.072 %w/w) were added to 30 g of dextran solution (1 g dextran in 29 g distilled water) to give a final ratio of 1:3.6:1000 w/w, respectively. Or, 19.5 g of aspirin solution (0.0924 %w/w) was added to 20.5 g of sulfadiazine and dextran solution (5 mg sulfadiazine and 1 g dextran in 19.5g distilled water) to give a final ratio of sulfadiazine: aspirin: dextran of 1:3.6:200 w/w. The molecular ratio of sulfadiazine to aspirin in both mixtures was 1:5. Three hundred microliters of these solutions were frozen in polypropylene sample tubes (10 mm diameter) by immersion in liquid nitrogen for 10 min, then dried at a vacuum level below 5 Pa for 23.5 h in a lyophilizer (Freezevac C-1, Tozai Tsusho Co., Tokyo). The shelf temperature was between −35 and −30°C for the first 1 h, 20°C for the subsequent 19 h, and 30°C for the last 3.5 h.

Lyophilized cephalothin formulations were prepared from an aqueous solution containing cephalothin and dextran (or MC). Two grams of aqueous cephalothin solution (0.125 %w/w) was added to 18 g of dextran (or MC) solution (0.5 g dextran (or MC) in 17.5g distilled water) to give a solution of cephalothin and dextran (or MC) (1:200 w/w). Three hundred microliters of the solution was freeze-dried as described above.

Lyophilized formulations were stored at 15°C for 24 h in a desiccator with a saturated solution of LiCl H_2O (12% relative humidity (RH)), potassium acetate (23.4%RH), K_2CO_3 $2H_2O$ (43%RH), NaBr $2H_2O$ (60.2%RH), or NaCl (75%RH). Water content was determined by the Karl Fisher method (684 KF Coulometer, Switzerland) and the results are shown in Tables 1 and 2.

Determination of the Acetyl Transfer Rate and the Hydrolysis Rate of Aspirin in Lyophilized Formulations

Lyophilized aspirin-sulfadiazine formulations in screw-capped polypropylene tubes were stored at temperatures ranging from 1°C to 80°C (±0.2°C at 1°C and ±0.1°C at 10–80°C). The samples were removed at appropriate intervals to determine the amount of remaining aspirin and sulfadiazine as well as their degradation products.

Samples were dissolved in 1 ml of 50 mM phosphate buffer (pH 2.5), and 0.7 ml of methanol containing 4-hydroxybenzoic acid as an internal standard was added in the solution. The solution was injected into an HPLC system consisting of a Shimadzu LC-10AD vp pump (Kyoto), a Shimadzu variable-wavelength UV detector (SDD-M10A) and a Shimadzu CLASS-VP data system. A Tosoh AS-8010 autoinjector (Tokyo) delivered 20-μL samples. The aspirin, sulfadiazine, salicylic acid and acetyl sulfadiazine were separated on a reversed-phase column (Tosoh TSK-GEL, 4.6 mm × 150 mm) maintained at 35°C. The detection wavelength was 260 nm for acetylsulfadiazine and 200 nm for the others. The mobile phase was a mixture of 50 mM phosphate buffer (pH 2.5) and methanol (3:2).

Table 2. Water Contents of Lyophilized Formulations Containing MC and Various Drugs

Relative humidity (%)	Water content (g/g of dry solid)	
	Bovine serum γ-globulin	Cephalothin
23.4	0.053 ± 0.001	0.056 ± 0.004
43	0.081 ± 0.003	0.083 ± 0.004
60.2	0.113 ± 0.006	0.111 ± 0.005

Determination of the Decomposition Rate of Cephalothin in Lyophilized Formulations

Lyophilized cephalothin formulations were stored at temperatures ranging from 10°C to 70°C and analyzed by HPLC in a manner similar to that described for aspirin. The internal standard was 4-aminobenzoic acid and the detection wavelength was 280 nm.

RESULTS

Acetyl Transfer between Aspirin and Sulfadiazine in Lyophilized Formulations Containing Dextran

Acetyl is transferred between aspirin and sulfadiazine in the solid-state (9). Figure 1 shows a time course typical of acetyl transfer in lyophilized formulations containing dextran. As levels of sulfadiazine and aspirin decreased, those of acetylsulfadiazine and salicylic acid increased. Since aspirin is also hydrolyzed in parallel with acetyl transfer in the presence of water (Scheme 1), the rate constant of acetyl transfer (k_T) and

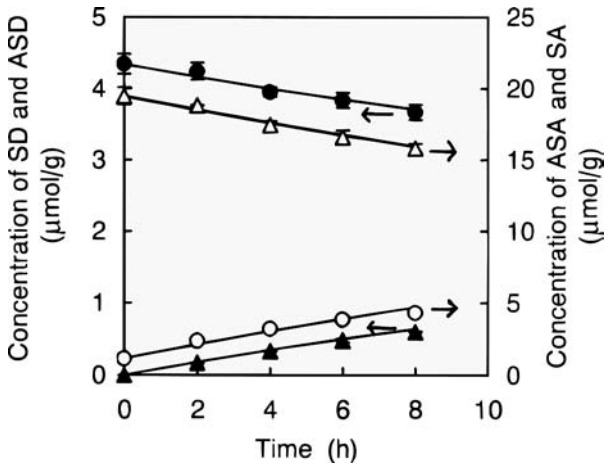


Fig. 1. Acetyl transfer reaction between aspirin and sulfadiazine in lyophilized formulations containing dextran at 50°C. Initial weight ratio of sulfadiazine:aspirin:dextran, 1:3.6:1000. Concentration of aspirin (△), sulfadiazine (●), acetyl sulfadiazine (▲), and salicylic acid (○). sd (n = 3).

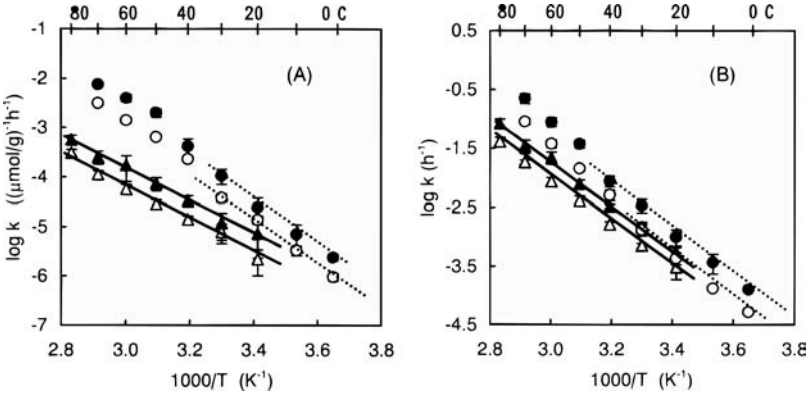
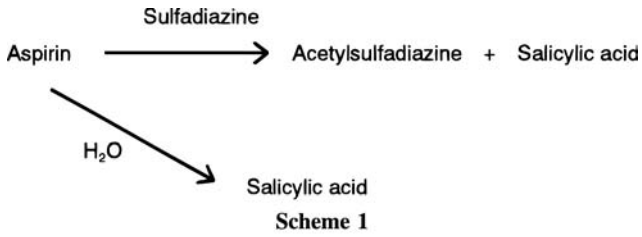


Fig. 2. Arrhenius plots for acetyl transfer between aspirin and sulfadiazine (A) and aspirin hydrolysis (B) in lyophilized formulations containing dextran. ○ Water activity, 0.6; initial weight ratio of sulfadiazine:aspirin:dextran, 1:3.6:200. ● Water activity, 0.6; initial weight ratio of sulfadiazine:aspirin:dextran, 1:3.6:1000. △ Water activity, 0.12; initial weight ratio of sulfadiazine:aspirin:dextran, 1:3.6:200. ▲ Water activity, 0.12; initial weight ratio of sulfadine:aspirin:dextran, 1:3.6:1000. sd (n = 3).

the pseudo rate constant of hydrolysis ($k_{H,pseudo}$) can be represented by following equations.



Scheme 1

$$d[SD]/dt = -k_T[SD][ASA]$$

$$d[ASA]/dt = -k_T[SD][ASA] - k_{H,pseudo}[ASA]$$

These rate constants (k_T and $k_{H,pseudo}$) calculated are shown as a function of temperature in Fig. 2. Only data representing less than 10% degradation were used for the calculation to avoid the effects of salicylic acid and acetic acid formation.

An increase in water activity increased both k_T and $k_{H,pseudo}$. At a water activity of 0.12 (stored at 12%RH), the Arrhenius plots of both acetyl transfer and aspirin hydrolysis were linear. In contrast, acetyl transfer exhibited temperature dependence with a distinct break around 40°C when the water activity was 0.6. The apparent activation energy of acetyl transfer was 15 and 21 kcal/mol at water activities of 0.12 and 0.6, respectively. The latter was calculated from the slope of rate constants at lower temperatures (dotted lines in Fig. 2A). The temperature dependence of aspirin hydrolysis at a water activity of 0.6 also showed a break around 40°C although it was less distinct than that of acetyl transfer (Fig. 2B). The apparent activation energy was 17 and 18 kcal/mol at water activities of 0.12 and 0.6, respectively.

Both k_T and $k_{H,pseudo}$ decreased when the weight ratio of aspirin and sulfadiazine to dextran increased. This may be because the calculated concentrations of aspirin and sulfadiazine used for the estimation of the rate constants (expressed by μ mol/g) differed from the actual concentrations that govern the reaction rate. The estimated rate constants were obtained from the calculated concentrations by assuming that diffusion occurs homogeneously in the formulations.

Although the T_{mc} of lyophilized formulations was not determined in this study, present systems can be considered to have similar T_{mc} values as the lyophilized formulations containing bovine serum γ-globulin, reported previously (8), ie. about 35°C at a water activity of 0.6, and higher than 80°C at a water activity of 0.12. This consideration is based on the findings that the T_{mc} was not significantly different for lyophilized dextran without γ-globulin (10) and that the lyophilized dextran formulation studied here contained small amounts of aspirin (1.8%w/w at the largest) and sulfadiazine (0.5%w/w at the largest). It is also based on the finding that the water contents of these formulations were quite similar as shown in Table 1. Therefore, the distinct break in the temperature dependence of acetyl transfer rate observed at a water activity of 0.6 appeared to correspond to the T_{mc}. At a water activity of 0.12, almost linear temperature dependence was observed at temperatures below T_{mc} for both the acetyl transfer rate and the aspirin hydrolysis rate.

Hydrolysis of Cephalothin in Lyophilized Formulations Containing Dextran or Methylcellulose

Cephalothin has a β-lactam bond and an ester bond that are both susceptible to hydrolysis (11). Figure 3 shows the time course of cephalothin hydrolysis in lyophilized formulations containing dextran or MC. The rate of cephalothin hydrolysis in lyophilized formulations containing MC was faster than that in formulations containing dextran at any water activity. Cephalothin hydrolysis in both formulations followed first-order kinetics. The temperature dependence of the apparent first-order rate constant is shown in Figs. 4 and 5, for the formulations containing dextran and MC, respectively. The apparent hydrolysis rate constants that were obtained in phosphate buffer (pH 7.4) (12) are also shown in Fig. 4. The hydrolysis rate constant in lyophilized formulations increased as water activity increased. The temperature dependence of the hydrolysis rates in both formulations containing dextran and MC appeared to be linear at any water activity in a manner similar to that of hydrolysis in aqueous solution. Interestingly, the estimated

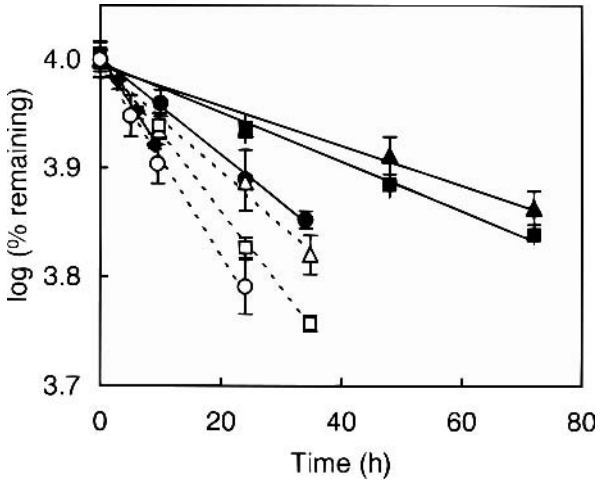


Fig. 3. Hydrolysis of cephalothin in lyophilized formulations containing dextran (closed) or methyl cellulose (open) at 50°C. Water activity: 0.23 (△▲), 0.43 (□■), 0.6 (○●) and 0.75 (♦). sd (n = 3).

apparent activation energy of cephalothin hydrolysis was between 23 and 26 kcal/mol for the lyophilized formulations containing dextran, and between 23 and 24 kcal/mol for those containing MC. These values are close to the apparent activation energy obtained for hydrolysis in solution (24 kcal/mol).

The T_{mc} of lyophilized dextran formulations with cephalothin should be around 20°C at a water activity of 0.75, 35°C at 0.6, and 55°C at 0.23 from the observed values of lyophilized dextran formulations with γ-globulin (8). Similarly, the assumed T_{mc} of lyophilized MC formulations with cephalothin is around 25°C at a water activity of 0.6, 55°C at 0.43, and higher than 80°C at 0.23. The temperature dependence of cephalothin hydrolysis in both formulations containing dextran and MC appeared to be linear regardless of T_{mc}.

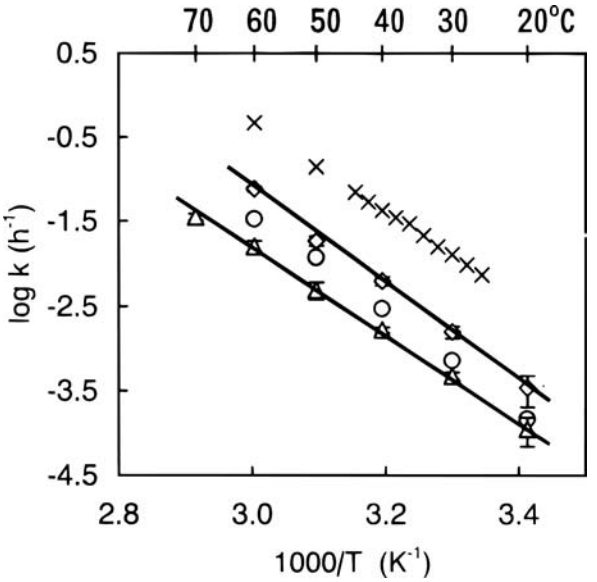


Fig. 4. Arrhenius plots for the hydrolysis of cephalothin in lyophilized formulations containing dextran (△○◇) and in solution (X). Water activity: 0.23 (△), 0.6 (○), and 0.75 (◇). sd (n = 3).

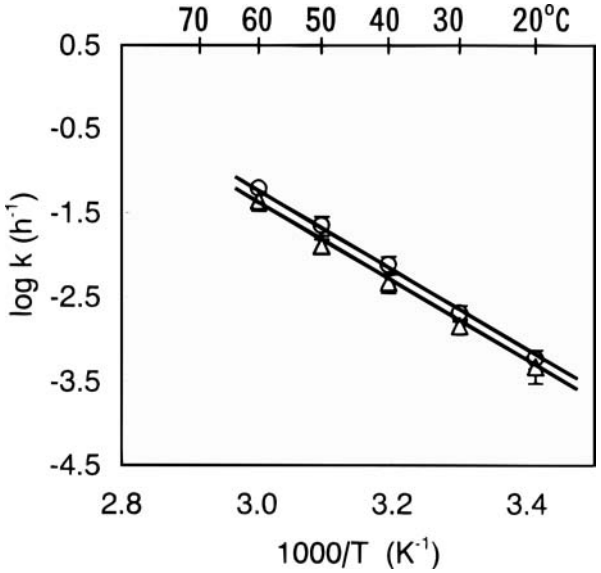


Fig. 5. Arrhenius plots for the hydrolysis of cephalothin in lyophilized formulations containing methyl cellulose. Water activity; 0.23 (△) and 0.6 (◯). sd (n = 3).

DISCUSSION

The Effect of T_{mc} on Hydrolysis Rates

The hydrolysis rate of cephalothin in lyophilized formulations containing dextran and MC increased with increasing water activity (Figs. 4 and 5). The increase in the hydrolysis rate of aspirin in lyophilized aspirin-sulfadiazine formulations containing dextran was similar (Fig. 2B). This can be ascribed to the contribution of water to the rate-limiting step as a reactant. In addition, the possibility of the medium effect of water changing polarity cannot be excluded (13). An increase in polarity may stabilize the transition state and increase the hydrolysis.

The temperature dependence of cephalothin hydrolysis in lyophilized formulations containing dextran and MC appeared to be linear regardless of their T_{mc}. The temperature dependence was also unaffected by the T_g of the formulations that are approximately 20 to 30°C higher than the T_{mc} (8). Since the translational mobility of drug and water molecules in lyophilized formulations is affected by T_g and/or T_{mc}, the hydrolysis rate should be affected by T_g and/or T_{mc} if the translational diffusion of the drug and/or water molecules is rate-limiting. The absence of a break in the temperature dependence around T_g and T_{mc} suggests that the translational diffusion is not rate-limiting. Since the translational diffusion of water can be considered to be much faster than that of the larger cephalothin molecule, the diffusion barrier of water molecules may be smaller than the activational barrier. It has been reported that water molecules possess high degree of translational mobility even in the glassy state (14).

The activation energy for the hydrolysis of cephalothin in the lyophilized formulations calculated from the slopes in Figs. 4 and 5 (23 to 26 kcal/mol) did not significantly differ from that for hydrolysis in solution (24 kcal/mol). The latter is coincident with the value reported for cephalothin hydrolysis at pH 5.00 (23 kcal/mol) (11). The lack of a significant difference in activation energy between lyophilized formulations and solutions supports the notion that the diffusion barrier of water

molecules is smaller than the activational barrier of the reaction. Thus, the hydrolysis rate of cephalothin in lyophilized formulations may not be affected by T_g and/or $T_{mc,}$ even if the translational mobility of water molecules changes around T_g and T_{mc}.

The temperature dependence of aspirin hydrolysis in lyophilized aspirin-sulfadiazine formulations containing dextran exhibited a small break around T_{mc} (Fig. 2B). This break cannot be ascribed to a change in the diffusion rate of water molecules, since the diffusion of water is not considered to be rate-limiting according to the results of cephalothin hydrolysis. Furthermore, the apparent activation energy of hydrolysis at temperatures below T_{mc} was 17 and 18 kcal/mol, which was very close to the value reported for the hydrolysis of aspirin in solution at pH 5 (17 kcal/mol) (15). This supports the notion that the diffusion of water is not rate-limiting. The hydrolysis of aspirin in neutral solutions is catalyzed by intramolecular general bases (16). Therefore, the small break around T_{mc} in the temperature dependence of aspirin hydrolysis may be due to the change in molecular mobility that is required for the critical conformational change of the intramolecular general base. The hydrolysis of cephalothin did not show such a break in the temperature dependence, suggesting that the type of molecular mobility that is critical for drug degradation largely depends on the degradation mechanisms.

The hydrolysis rate of aspirin in hydroxypropyl-β-cyclodextrin/aspirin complex substantially changed at T_g (4), which is much larger than that observed at T_{mc} in the lyophilized aspirin-sulfadiazine formulation containing dextran studied here. This difference may be due to the contribution of inclusion complexes in the former.

The Effect of T_{mc} on Acetyl Transfer Rates

The temperature dependence of acetyl transfer between aspirin and sulfadiazine in lyophilized formulations containing dextran exhibited a distinct break around T_{mc}. The translational mobility of aspirin and sulfadiazine can be considered to be lower than that of water because they are larger molecules. Thus, the diffusion barrier would become comparable to the activational barrier of the reaction. The change in the diffusion rate of these molecules around T_{mc} may reflect on the acetyl transfer rate, resulting in nonlinear temperature dependence with a distinct break.

The apparent activation energy of acetyl transfer at temperatures below T_{mc} was 21 kcal/mol at a water activity of 0.6, and 15 kcal/mol at a water activity of 0.12. An activation energy much larger than that obtained in this study (44 kcal/mol) for acetyl transfer between aspirin and sulfadiazine has been reported, but this value is for crystalline solids without water (9). Crystalline solids can be considered to require additional energy to break the lattice structure to undergo the reaction.

CONCLUSIONS

Acetyl transfer in lyophilized asprin-sulfadiazine formulations containing dextran, a bimolecular reaction, exhibited a temperature dependence with a distinct break around T_{mc}. This may be ascribed to a change in the translational mobility of aspirin and sulfadiazine molecules around T_{mc}. The hydrolysis of cephalothin and aspirin in lyophilized formulations, which is also a bimolecular reaction, was not associated with a distinct break. This suggests that water diffusion is not rate-limiting in that the reaction rate was not significantly affected by the change in the diffusion rate of water around T_{mc}. The diffusion barrier of water molecules in lyophilized formulations can be considered to be smaller than the activational barrier of the hydrolysis of cephalothin and aspirin, whereas the diffusion barrier of aspirin and sulfadiazine molecules becomes comparable to the activational barrier of the acetyl transfer reaction between aspirin and sulfadiazine.

REFERENCES

1. S. L. Shamblin, X. Tang, L. Chang, B. C. Hancock, and M. J. Pikal. Characterization of the time scales of molecular motion in pharmaceutically important glasses. *J. Phys. Chem.* **103**:4113–4121 (1999).
2. V. Andronis and G. Zografi. The molecular mobility of supercooled amorphous indomethacin as a function of temperature and relative humidity. *Pharm. Res.* **15**:835–842 (1998).
3. Y. Guo, S. R. Byrn, and G. Zografi. Physical characteristics and chemical degradation of amorphous quinapril hydrochloride. *J. Pharm. Sci.* **89**:128–143 (2000).
4. S. P. Duddu and K. Weller. Importance of glass transition temperature in accelerated stability testing of amorphous solids: Case study using a lyophilized aspirin formulation. *J. Pharm. Sci.* **85**:345–347 (1996).
5. L. Streefland, A. D. Auffret, and F. Franks. Bond cleavage reactions in solid aqueous carbohydrate solutions. *Pharm. Res.* **15**:843–849 (1998).
6. M. C. Lai, M. J. Hageman, R. L. Schowen, R. T. Borchardt, and E. M. Topp. Chemical stability of peptides in polymers. 1. Effect of water on peptide deamidation in poly(vinyl alcohol) and poly(-vinyl pyrrolidone) matrixes. *J. Pharm. Sci.* **88**:1073–1080 (1999).
7. M. C. Lai, M. J. Hageman, R. L. Schowen, R. T. Borchardt, and E. M. Topp. Chemical stability of peptides in polymers. 2. Discriminating between solvent and plasticizing effects of water on peptide deamidatin in poly(vinylpyrrolidone). *J. Pharm. Sci.* **88**:1081–1089 (1999).
8. S. Yoshioka, Y. Aso, and S. Kojima. The effect of excipients on the molecular mobility of lyophilized formulations, as measured by glass transition temperature and NMR relaxation-based critical mobility temperature. *Pharm. Res.* **16**:135–140 (1999).
9. L. Liu and E. L. Parrott. Solid-state reaction between sulfadiazine and acetylsalicylic acid. *J. Pharm. Sci.* **80**:564–566 (1991).
10. S. Yoshioka, Y. Aso, S. Kojima, S. Sakurai, T. Fujiwara, and H. Akutsu. Molecular mobility of protein in lyophilized formulations linked to the molecular mobility of polymer excipients, as determined by high resolution ^{13}C solid-state NMR. *Pharm. Res.* **16**:1621–1625 (1999).
11. T. Yamana and A. Tsuji. Comparative stability of cephalosporins in aqueous solutions: Kinetics and mechanisms of degradation. *J. Pharm. Sci.* **65**:1563–1574 (1976).
12. Y. Aso, T. Sufang, S. Yoshioka, and S. Kojima. Amount of mobile water estimated from ^{2}H spin-lattice relaxation time, and its effects on the stability of cephalothin in mixtures with pharmaceutical excipeints. *Drug Stability* **1**:237–242 (1997).
13. E. Y. Shalaev and G. Zografi. How does residual water affect the solid-state degradation of drugs in the amorphous state? *J. Pharm. Sci.* **85**:1137–1141 (1996).
14. C. A. Oksanen and G. Zografi. Molecular mobility in mixtures of absorbed water and solid poly(vinylpyrrolidone). *Pharm. Res.* **10**:791–799 (1993).
15. E. R. Garrett. The kinetics of solvolysis of acyl esters of salicylic acid. *J. Am. Chem. Soc.* **79**:3401–3408 (1957).
16. A. R. Fersht and A. J. Kirby. The hydrolysis of aspirin. Intramolecular general base catalysis of ester hyddrolysis. *J. Am. Chem. Soc.* **89**:4857–4863 (1967).