Relationship between Water Mobility, Measured as Nuclear Magnetic Relaxation Time, and the Crystallization Rate of Amorphous Nifedipine in the Presence of Some Pharmaceutical Excipients

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The crystallization rates of fused nifedipine in 6 mixtures with different polymeric pharmaceutical excipients were each measured as a function of the water content using an isothermal microcalorimeter. In all the excipients studied, the crystallization rate increased as the water content increased, but the extent of the increase in crystallization rate varied with the excipient. The spin-lattice relaxation rates ($1/T_1$) of deuterium oxide absorbed by the mixtures suggested that water mobility differed according to the excipient even if water content of the mixtures was the same. The crystallization rate of mixtures with crystalline cellulose, methyl cellulose, cornstarch and polyvinyl alcohol correlated with the $1/T_1$ values. It is suggested that the difference in crystallization rate among the excipients can be explained by the water mobility which is governed by the interaction between water and excipient molecules. Increase in the mobility of water in the mixtures may decrease the nifedipine matrix viscoelasticity through the plasticizing effect of water, resulting in an increase in the crystallization rate. The plasticizing effect of water was confirmed by measuring nifedipine mobility in a sample without excipients. The nifedipine mobility, determined by measuring the spin–spin relaxation time of protons in fused nifedipine increased as the water content increased.

Key words mobility; nuclear magnetic relaxation time; water; nifedipine; crystallization

The importance of water mobility for drug stability has been pointed out.[1–5] We previously reported that the cephalothin hydrolysis rates in mixtures with microcrystalline cellulose and cornstarch were affected not only by the water contents of the mixtures but also by the mobility of the water molecules, measured as the ^2H spin–lattice relaxation time (T_1).[5] Water mobility was found to be an important factor affecting the chemical stability of cephalothin-excipient mixtures. In the present study, nifedipine crystallization was chosen as a model to study the effects of water mobility on the physical stability of drugs, as amorphous nifedipine crystallizes at temperatures above its glass transition temperature depending on its water content, and its crystallization rate can be measured easily using an isothermal microcalorimeter as described.[6]

In this paper, we describe the relationship between water mobility, measured as T_1, and the crystallization rate of amorphous nifedipine in physical mixtures with some polymeric pharmaceutical excipients as a function of their water contents, and discuss the difference in the crystallization rate with the excipients in relation to the water mobility in the mixtures. The plasticizing effect of water is also discussed in terms of nifedipine mobility, measured as the spin–spin relaxation time of nifedipine protons.

Experimental

Materials Nifedipine, crystalline cellulose (MCC) and cornstarch (STA) were purchased from Sigma (St. Louis, MO), Merck (Darmstadt) and Kosakai Pharmaceutical (Tokyo), respectively. Soluble starch (SSTA), methyl cellulose (MC), polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) were obtained from Wako (Osaka). MCC and STA were dried at 100 °C for 4 h before use. PVP was dried at room temperature over P_2O_5 for 1 week and the other excipients were used as received. Fused nifedipine was prepared as described previously[6]; briefly, it was heated at 180 °C for 20 min and then cooled by immersion in liquid nitrogen. The resulting fused nifedipine was mixed with each excipient using a mortar and pestle and each mixture was stored in an amber glass vessel at −15 °C until required for use. The heat production by nifedipine-excipient mixtures was almost the same as that by fused nifedipine indicating that change in the crystallinity of fused nifedipine by mixing with the excipients was negligible. All the other chemicals used were of reagent grade. All the experiments were carried out in a dark room (<20 lux), the temperature and relative humidity (RH) of which were maintained at 25±1 °C and <50%, respectively.

Isothermal Microcalorimetry Heat production by fused nifedipine in physical mixtures with polymeric pharmaceutical excipients of various water contents was measured using an isothermal microcalorimeter (model 2277, Thermometric AB, Sweden) at 50 °C, as described.[5] About 20 mg of the mixture was weighed in a 3-ml glass vial, which was maintained at 25 °C and 11—75% RH with the seal off for 1 h to adjust the water content of the mixture. The vial was sealed, placed in the equilibration position of the microcalorimeter for 10 min and then lowered to the measuring position of the instrument. The microcalorimeter output was collected using a computer (model 9801VM, NEC, Tokyo) by means of an AD converter (model EC-2325, Elmec Inc. Limited, Tokyo).

Determination of the Water Contents of the Fused Nifedipine-Excipient Mixtures Twenty-mg samples of each fused nifedipine-excipient mixture were weighed into 3-ml isothermal calorimetry glass vials and maintained at 25 °C and 11—75% RH for 1 h. Each vial was sealed, 1 ml anhydrous methanol was added through a rubber septum, and the mixture was allowed to stand for 4 h to extract the water in the methanol, the content of which was determined by the Karl Fischer method using a coulometric Karl Fischer titrater (model 684, Metrohm, Switzerland).

Nuclear Magnetic Resonance (NMR) Measurement The spin–lattice relaxation time of deuterium oxide in each fused nifedipine-excipient mixture was determined using a NMR spectrometer (VXR400RS, Varian) at 61.4 MHz. The inversion recovery method was used with 15 μs of 90° pulse duration. The measurement was repeated 128 times with 200 ms of recycling time. Each mixture was kept at 25 °C for 1 h in the presence of an appropriate saturated salt solution in deuterium oxide to control the RH of the atmosphere. The mixture was transferred to a glass tube (4 mm outer diameter and 20 mm long), which was put into a 5-mm NMR sample tube and measurement was carried out at 50 °C. Sample preparation and measurement were repeated 3 times, and the average of the T_1 values was reported. The mobility of water absorbed by the excipients studied may lie within an extremely narrow limit, because T_1 increased with increasing NMR measurement temperature.

The relative mobility of nifedipine molecules in the absence of excipient was measured. The spin–spin relaxation time (T_2) of the nifedipine

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protons was used as a measure of the molecular mobility and was determined by analyzing the free induction decay (FID) of nifedipine protons. Fused and crystalline nifedipine samples were stored at 50 °C and 13—60% RH for 1 h, after which the on-resonance FID of the nifedipine protons was measured at 25 MHz using a pulse NMR spectrometer (JNM-MU25, JEOL, Tokyo). The 90° pulse durations were 2 μs, and measurement was carried out at 50 °C. The "solid echo" method[7] was used in the detection stage to overcome the effects of dead-time with an echo decay of 10 μs. The FID signals were analyzed using a non-linear, least-squares fitting program. The relative standard deviation of T_2 values was less than 5%.

Results and Discussion

Fused nifedipine in the physical mixtures with all the excipients studied exhibited considerable heat production. Figure 1 shows a typical time profile of heat production by fused nifedipine-STA mixtures (solid line). The observed heat production was considered to be the heat of crystallization of amorphous nifedipine and that of polymorphic transition to the stable crystalline form, as reported previously.[6] The ratio of nifedipine crystallized to initial amorphous nifedipine in each mixture at a certain time was calculated by dividing the area under the heat production–time curve from time zero to that time by the total area under the curve.[6] The amount of amorphous nifedipine remaining is shown by the dashed line in Fig. 1. The time required for half the amorphous nifedipine to become crystalline, t_{50}, was calculated from the time profile of amorphous nifedipine remaining. The reciprocal of t_{50} ($1/t_{50}$) was used as a measure of the crystallization rate as reported previously.[6]

Figure 2 shows the effect of water content on the crystallization rate of fused nifedipine mixed with various excipients. With all the mixtures studied, the crystallization rate, represented by $1/t_{50}$, increased as the water content increased, but the extent of increase in the crystallization rate in each mixture differed, indicating that the crystallization rate of fused nifedipine in mixtures with the same water content varied according to the excipient. The crystallization rate of the nifedipine-MCC mixture with a water content of 0.04 g/g dry solid was about four times higher than that of a STA mixture with the same water content. Figure 3 shows the effect of water content on the spin–lattice relaxation rate ($1/T_1$) of deuterium oxide absorbed by the fused nifedipine-excipient mixtures. The $1/T_1$ decreased as the water content increased with all the excipients studied, but the $1/T_1$ values of mixtures with the same water content differed according to the excipient. The $1/T_1$ of a MCC mixture with a water content of 0.04 g/g dry solid was different from that of a STA mixture with the same water content, similar to the crystallization rate findings. The crystallization rates of fused nifedipine in the various mixtures were plotted against the $1/T_1$ values, as shown in Fig. 4. With the STA, MCC, MC and PVA mixtures, the crystallization rate increased as the $1/T_1$ decreased and the data points could be described by a single correlation curve, indicating that the crystallization rate was related to the water mobility, measured as $1/T_1$. The decrease in $1/T_1$ indicates decrease in correlation time of water molecules, or increase in water molecule mobility. Increased water mobility in the mixtures may decrease the nifedipine matrix

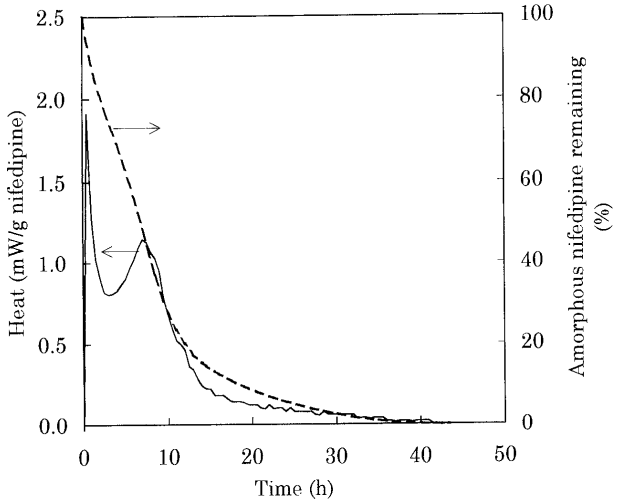

Fig. 1. Typical Time Profiles of Heat Production (——) by Fused Nifedipine-Cornstarch Mixtures and Amorphous Nifedipine Remaining (– – –) in the Mixtures

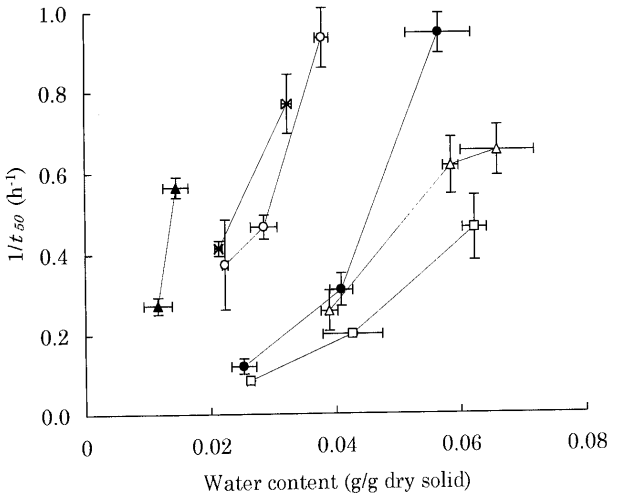

Fig. 2. Effect of Water Content on the Crystallization Rate of Nifedipine in Fused Nifedipine-Excipient Mixtures

△, STA; ●, SSTA; ○, MCC; ×, MC; □, PVP; ▲, PVA. The error bar in the figure represents the standard deviation of three experiments.

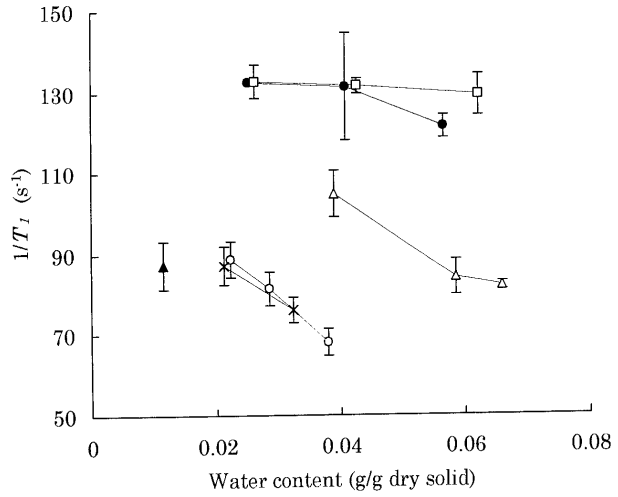

Fig. 3. Effect of Water Content on the Spin-Lattice Relaxation Rate ($1/T_1$) of Deuterium Oxide Absorbed by the Fused Nifedipine-Excipient Mixtures

△, STA; ●, SSTA; ○, MCC; ×, MC; □, PVP; ▲, PVA. The error bar in the figure represents the standard deviation of three experiments.

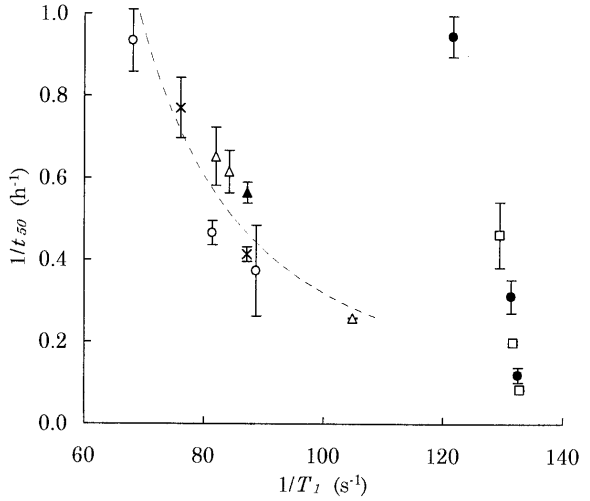

Fig. 4. Relationship between the Crystallization Rate of Nifedipine and Spin-Lattice Relaxation Rate

△, STA; ●, SSTA; ○, MCC; ×, MC; □, PVP; ▲, PVA. The error bar in the figure represents the standard deviation of three experiments.

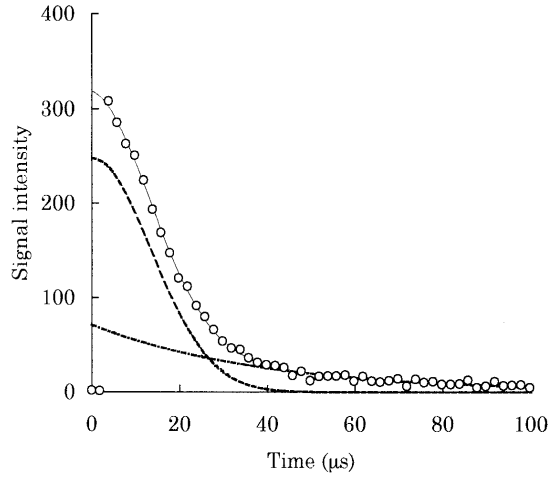

Fig. 5. Typical On-Resonance FID Signal from the Fused Nifedipine Obtained by the Solid Echo Pulse Sequence Method (○) and the Calculated Curve (——) Obtained by Least-Squares Fitting

The separate decay components are: – – –, Gaussian; –·–·–, Lorentzian.

viscoelasticity through the plasticizing effect of water, resulting in an increase in the crystallization rate. It is not clear why the PVP and SSTA mixtures showed different T_1 dependencies of their crystallization rates from the STA, MCC, MC and PVA mixtures, although it may have been due to rapid exchange of deuterium with polymer protons or direct effect of these excipients, such as solubilization of fused nifedipine by moisture absorption of excipients.

The plasticizing effect of water was confirmed by measuring the mobility of nifedipine molecules in a fused nifedipine sample without excipients. The relative mobility of nifedipine molecules was estimated from the spin–spin relaxation time (T_2) of protons of fused nifedipine stored under various RH conditions. The T_2 of nifedipine protons was obtained by on-resonance free induction decay (FID) analysis. Figure 5 shows a typical on-resonance FID signal, measured by "solid echo" pulse sequence method,[7] from

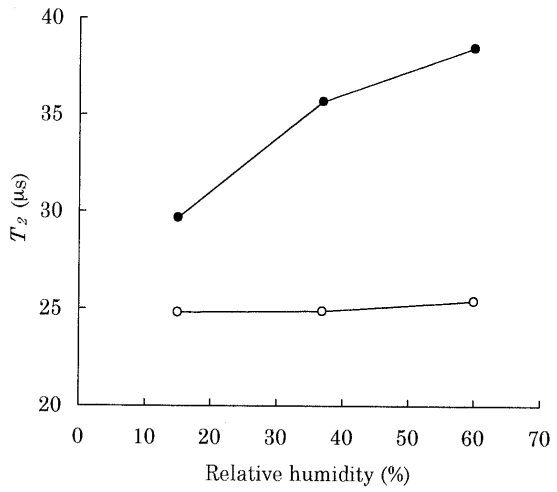

Fig. 6. Effect of Relative Humidity on the Spin–Spin Relaxation Time of Lorentzian Decay Component of Crystalline (○) and the Fused Nifedipine (●)

nifedipine protons. The observed FID signal was attributed to nifedipine protons, as similar FID signals were obtained from nifedipine samples stored under water and deuterium oxide atmospheres. The T_2 of nifedipine protons was calculated from the FID, based on the assumption that the decay was comprised of Gaussian ($e^{-1/2(t/T_2)^2}$) and Lorentzian (e^{-t/T_2}) decay components. The FID was measured with fused and crystalline nifedipine stored under various RH conditions. Figure 6 shows the effect of RH on the T_2 of the component which exhibited Lorentzian decay. The T_2 of crystalline nifedipine was independent of the water content, suggesting that the mobility of crystalline nifedipine was not affected by water due to its rigid crystalline structure. However, the T_2 of fused nifedipine increased as the RH increased, indicating that water increased the mobility of nifedipine molecules in fused nifedipine matrices; in other words, water decreased the matrix viscoelasticity, resulting in acceleration of nifedipine crystallization.

In conclusion, the crystallization rate of nifedipine in admixtures with some pharmaceutical excipients correlated with the water mobility, measured as spin–lattice relaxation time of deuterium oxide. This finding indicates that water mobility affects the physical, as well as the chemical, stability of drugs.

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