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Note

Crystallization rate of amorphous nifedipine analogues unrelated to the glass transition temperature

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Abstract

To examine the relative contributions of molecular mobility and thermodynamic factor, the relationship between glass transition temperature (T_g) and the crystallization rate was examined using amorphous dihydropyridines (nifedipine (NFD), *m*-nifedipine (*m*-NFD), nitrendipine (NTR) and nilvadipine (NLV)) with differing T_g values. The time required for 10% crystallization, t_{90}, was calculated from the time course of decreases in the heat capacity change at T_g. The t_{90} of NLV and NTR decreased with decreases in T_g associated with water sorption. The t_{90} versus T_g/T plots almost overlapped for samples of differing water contents, indicating that the crystallization rate is determined by molecular mobility as indicated by T_g. In contrast, differences in the crystallization rate between these four drugs cannot be explained only by molecular mobility, since the t_{90} values at a given T_g/T were in the order: NLV > NTR > NFD ≈ *m*-NFD. A lower rate was obtained for amorphous drugs with lower structural symmetry and more bulky functional groups, suggesting that these factors are also important. Furthermore, the crystallization rate of NTR in solid dispersions with poly(vinylpyrrolidone) (PVP) and hydroxypropyl methylcellulose (HPMC) decreased to a greater extent than expected from the increased T_g. This also suggests that factors other than molecular mobility affect the crystallization rate.

Keywords: Crystallization; Amorphous state; Nifedipine; Glass transition; Molecular mobility; Excipients

Preparation of poorly water-soluble pharmaceuticals into amorphous forms improves their solubility. However, amorphous solids are physically unstable because of their high energy state, and crystallization during storage presents a problem. The process of crystallization is known to comprise two major steps: nucleation and crystal growth, and the rates are generally governed by molecular mobility affecting the diffusion rate of molecules and thermodynamic factors such as the Gibbs free energy and nucleus/amorphous interfacial energy (Saleki-Gerhardt and Zografi, 1994; Hancock and Zografi, 1997; Rodríguez-Hornedo and Murphy, 1999; Andronis and Zografi, 2000; Ngai et al., 2000). Our previous studies demonstrated that the overall crystallization rate of nifedipine (NFD) for both the amorphous pure drug and solid dispersions with poly(vinylpyrrolidone) (PVP) had similar temperature dependence as the mean relaxation time calculated using the Adam-Gibbs-Vogel equation, suggesting that the molecular mobility of amorphous pharmaceuticals was one of the important factors affecting the crystallization rate (Aso et al., 2001, 2004). However, the crystallization rate of amorphous pharmaceuticals cannot be determined only by molecular mobility, as it has been reported that the susceptibility to crystallization of pharmaceuticals possessing quite different thermodynamic properties does not follow the order of the decrease in the glass transition temperature (T_g) (Zhou et al., 2002).

The purpose of the present study is to discuss the relative contributions of the molecular mobility and thermodynamic factors to the crystallization rates of dihydropyridines with different substituents, including NFD, *m*-nifedipine (*m*-NFD), nitrendipine (NTR) and nilvadipine (NLV) (Fig. 1). The overall crystallization rates of these drugs in the pure amorphous solids were measured under various relative humidity (RH) conditions to elucidate the effects of the substituents and water content on the crystallization rate. The crystallization rate of NTR was also determined in solid dispersions containing polymers (PVP and hydroxypropyl methylcellulose (HPMC)). Although some

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	abbreviation	R_1	R_2	R_3	R_4
nifedipine	[NFD]	CH_3	CH_3	NO_2	H
m-nifedipine	[m-NFD]	CH_3	CH_3	H	NO_2
nitrendipine	[NTR]	CH_3	C_2H_5	H	NO_2
nilvadipine	[NLV]	CN	$(CH_3)_2CH$	H	NO_2

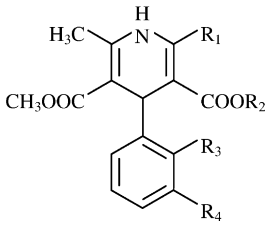

Fig. 1. Chemical structures of dihydropyridines.

papers have dealt with the crystallization of NTR and NLV in solid dispersions (Hirasawa et al., 2003a,b, 2004; Wang et al., 2005, 2006), few data are available that allow quantitative discussion about the relationship between molecular mobility and crystallization rates.

NFD and HPMC (USP grade) were purchased from Sigma Chemical Co. NTR, *m*-NFD and PVP (weight average molecular weight of 40000) were obtained from Wako Pure Chemical Industries Ltd. NLV was kindly supplied by Astellas Pharma Inc. The amorphous NFD, *m*-NFD, NTR, NLV and NTR solid dispersions with PVP and HPMC were prepared by melt quenching in the cell of a differential scanning calorimeter (DSC2920, TA Instruments). The crystalline drug or mixture of NTR and polymer (5 mg) was melted at a temperature approximately 20 °C above its melting point and then cooled to approximately 100 °C below the T_g at a cooling rate of 40 °C/min. Thermal and photo degradation of the drugs was checked by HPLC, and no change in the chromatograms was observed after the preparation in comparison with that before. Fig. 2 shows typical DSC thermograms for the four amorphous drugs immediately after preparation and after subsequent storage. The T_g values for the amorphous drugs were: NLV, 48.6 ± 0.3 °C; NFD, 46.2 ± 0.2 °C; *m*-NFD, 41.3 ± 0.1 °C; NTR, 32.4 ± 0.3 °C. As shown in Fig. 2(b), freshly prepared amorphous NFD exhibited two endothermic peaks at around 161 °C and 168 °C. The two melting points of the peaks agreed well with that for the metastable form II and stable form I, respectively (Burger and Koller, 1996). As shown in Fig. 2(c), the NFD sample, retaining an amorphous portion after 5 h storage at 60 °C, showed exothermic peaks due to crystallization of the amorphous phase and its transformation into a stable crystal, and melted at 168 °C, which is approximately the same temperature as the melting point of the intact crystal. As shown in Fig. 2(d), the sample stored at 60 °C for 46 h showed the exothermic peak around 120–140 °C due to transformation into a stable crystal, although change in the heat capacity (ΔC_p) at T_g was not significant. The exothermic peak around 120–140 °C due to transformation into a stable crystal was also observed during storage at 50 °C and 70 °C (thermogram not shown). These DSC thermograms suggested that amorphous NFD initially crystallized into a metastable form. Crystallization into the metastable form was also observed during storage at 50 °C and 70 °C (thermogram not shown). Amorphous *m*-NFD showed an exothermic peak due to crystallization but no obvious peak due to transformation into a stable form like that shown by the NFD samples, and melted at 206 °C, which is approximately the same temperature as the melting point of intact *m*-NFD (Fig. 2(f) and (g)). It is not clear from the DSC thermograms whether transition to a stable or a metastable crystalline form occurred during storage. Fig. 2(j) and (k) show the DSC thermograms of the partially crystallized NTR samples showing one melting peak at 128 °C. The observed melting point was lower than that of the stable crystal

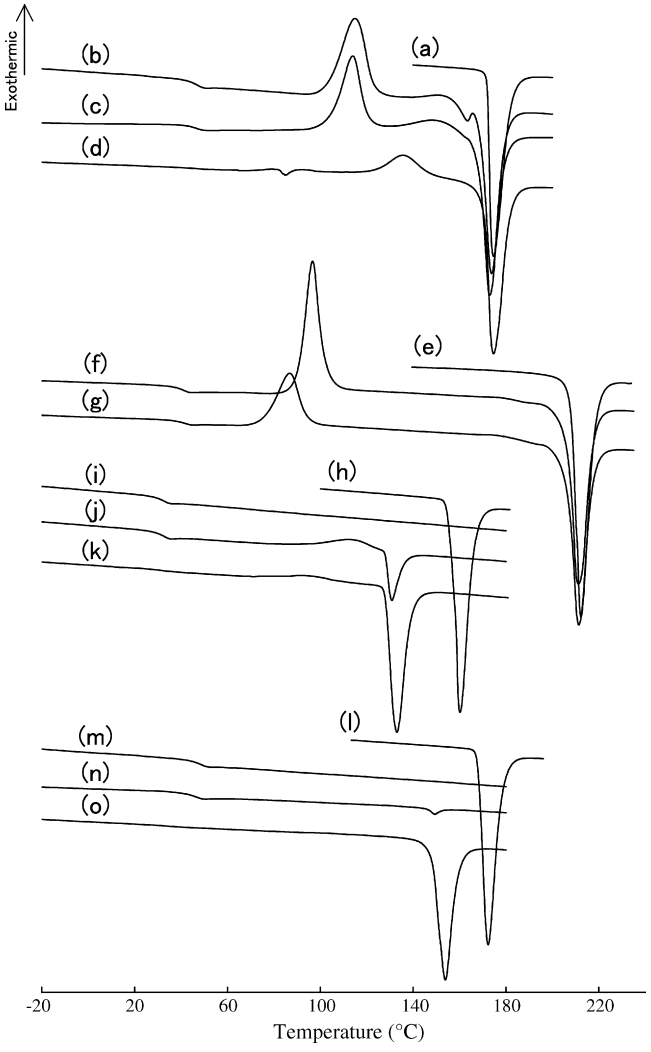

Fig. 2. Typical DSC thermograms: (a) NFD crystalline in the stable form, (b) freshly prepared amorphous NFD, (c) amorphous NFD after 5h-storage at 60 °C (d) amorphous NFD after 46 h-storage at 60 °C, (e) m-NFD crystalline in the stable form, (f) freshly prepared amorphous m-NFD, (g) amorphous m-NFD after 15 h-storage at 50 °C, (h) NTR crystalline in the stable form, (i) freshly prepared amorphous NTR, (j) amorphous NTR after 2 h-storage at 60 °C, (k) amorphous NTR after 9.75 h-storage at 60 °C, (l) NLV crystalline in the stable form, (m) freshly prepared amorphous NLV, (n) amorphous NLV after 48 h-storage at 80 °C, (o) amorphous NLV after 168 h-storage at 80 °C. Heating rate: 20 °C/min.

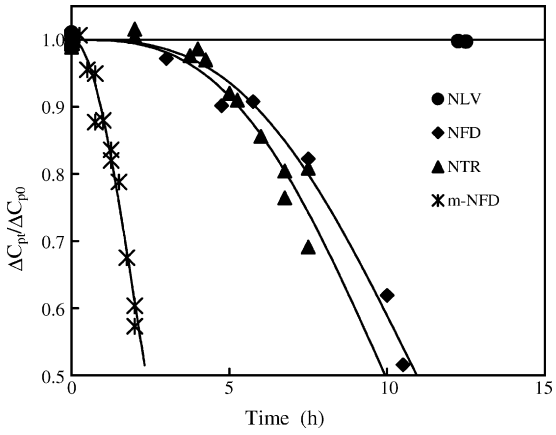

Fig. 3. Time profiles of crystallization for four dihydropyridines at 60 °C and 0%RH. The ratio of the amorphous form remaining at time t was calculated from the ΔC_p value assuming that the amount of amorphous phase is proportional to the ΔC_p. ΔC_{p0} and ΔC_{pt} are changes in ΔC_p at time 0 and t, respectively. Solid lines denote the fitting to the Avrami equation ($x(t) = \exp[-kt^n]$, $n = 3$).

Table 1
T_g values of amorphous NLV and NTR

RH (%)	T_g (°C)	
	NLV	NTR
0 (P_2O_5)	48.6 ± 0.3	32.4 ± 0.3
12 ($LiCl{\cdot}2H_2O$)	48.1 ± 0.7	30.5 ± 0.4
25 (CH_3COOK)	46.4 ± 0.5	29.0 ± 0.3
43 ($K_2CO_3{\cdot}2H_2O$)	43.4 ± 0.4	25.8 ± 0.3

For water absorption, the samples were kept at 5 °C for approximately 50 h in a desiccator containing saturated salt solutions. No crystallization was observed during the water absorption, as indicated by no endothermic melting peak in DSC thermograms.

(158 °C) and consistent with that reported for a metastable crystal (Kuhnert-Brandstätter and Völlenklee, 1986; Burger et al., 1997). As shown in Fig. 2(n) and (o), the partially crystallized NLV samples showed one melting peak at 148 °C. The observed melting point was lower than that for a stable crystal (168 °C) and similar to that for the dehydrated form of the monohydrate (Hirayama et al., 2000). Both amorphous NTR and NLV samples were considered to crystallize to their metastable crystalline forms under the conditions studied.

Fig. 3 shows the time profiles of crystallization of NFD, *m*-NFD, NTR, NLV at 60 °C and 0%RH. The crystallization rate was in the order: NLV < NTR = NFD < *m*-NFD. Fig. 4 shows the temperature dependence of the time required for 10% crystallization (t_{90}). Although NFD and NLV have approximately the same T_g, their values of t_{90} at the same temperature differed by more than two orders of magnitude (Fig. 4(A)). As shown in Fig. 4(B), the value of t_{90} at a given T_g/T (T being storage temperature) was in the order: NLV > NTR > NFD ≈ *m*-NFD within the whole range of temperature studied. As shown in Fig. 1, the four dihydropyridines have various alkyl groups at one of the carbonylester positions (R_2), and differ in the substitution position of the nitro group in the phenyl moiety (R_3 or R_4). The bulkiness of R_2 shows the order: NFD, *m*-NFD (methyl) < NTR (ethyl) < NLV (isopropyl). Furthermore, the substituent at R_1 is a cyano group in NLV, whereas it is a methyl group in the other three drugs; thus, the structural symmetry of NLV is lower. Since the plots for NFD and *m*-NFD in Fig. 4(B) almost overlapped each other, the difference in the crystallization rate may be attributed to the difference in molecular mobility. In contrast, differences in the crystallization rate between NLV, NTR and NFD cannot be explained only by the difference in molecular mobility. The differences in structural symmetry and bulkiness of functional group may cause differences in the Gibbs free energy and nucleus/amorphous interfacial energy, resulting in the differing crystallization rates between these drugs.

The crystallization rate of amorphous NLV and NTR solids with differing T_g values due to differing water content was measured to elucidate the effect of T_g on the crystallization rate (Table 1). The partially crystallized NLV and NTR in the presence of water showed an endothermic melting peak at approximately 150 °C and 130 °C, respectively. This suggests that amorphous NLV and NTR containing water also crystallize into their metastable forms in a similar manner as shown for dry samples. Fig. 5(A) shows the temperature dependence of the t_{90} obtained for NLV and NTR in the presence of water. When compared at the same temperature, the t_{90} value decreased with increasing RH. As shown in Fig. 5(B), the t_{90} versus T_g/T plots for each drug overlapped with those obtained under dry conditions, suggesting that the effect of water on the t_{90} value was explainable by the plasticizing effect of absorbed water,

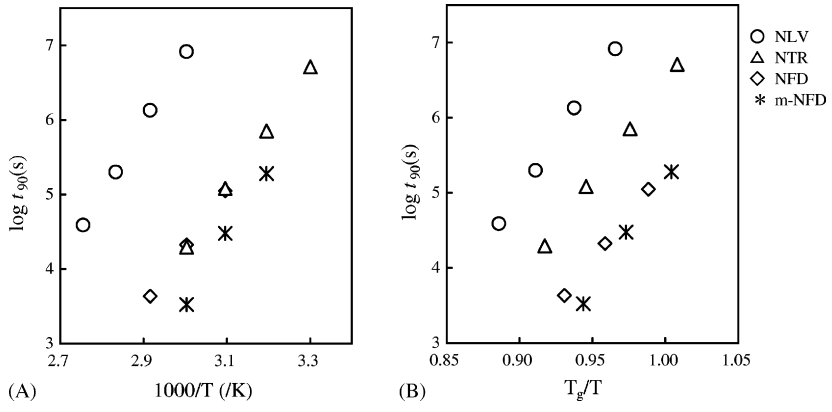

Fig. 4. Relationship between t_{90} for crystallization of drugs and storage temperature under dry conditions.

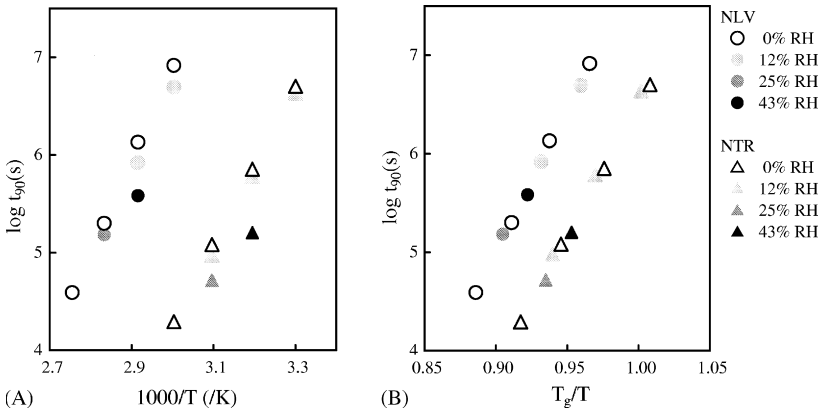

Fig. 5. Effect of absorbed water on the t_{90} of crystallization for NLV (circles) and NTR (triangles). The t_{90} values were measured at the early stage of crystallization at which no marked change in Tg was evident.

Table 2
T_g values of NTR-polymer solid dispersions

Polymer (%)	T_g (°C)	
	PVP	HPMC
0	32.4 ± 0.3	
3	33.2 ± 0.2	32.4 ± 0.1
5	34.1 ± 0.3	32.9 ± 0.4
6	34.1 ± 0.3	32.8 ± 0.2
11	36.6 ± 0.3	33.4 ± 0.3
20	–	33.7 ± 0.7
23	43.4 ± 0.8	–

similarly to that reported for NFD crystallization (Aso et al., 1995).

The effect of T_g on the crystallization rate of NTR was also investigated in solid dispersions with PVP and HPMC. A single T_g was observed for amorphous NTR-polymer solid dispersions prepared with 2.7–23% polymer excipients, indicating that NTR and polymer are miscible within the sensitivity limit of the DSC method. The value of T_g tended to increase with the amount of polymer, and the extent of increase was greater for NTR-PVP dispersions than for NTR-HPMC dispersions (Table 2). As the partially crystallized NTR-polymer dispersions showed a melt-

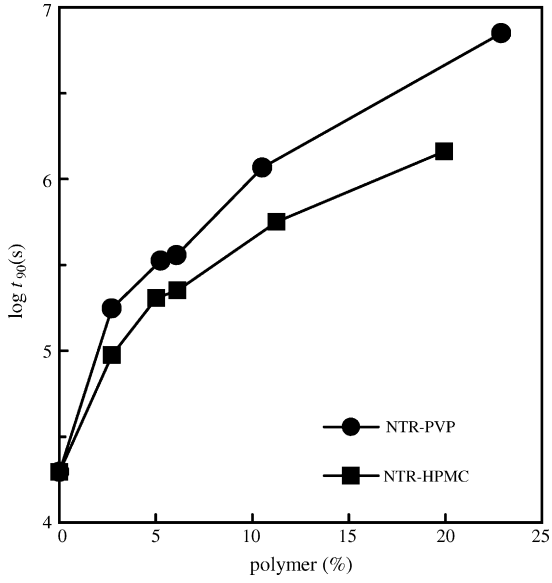

Fig. 6. Effect of polymer content on crystallization of NTR in solid dispersions with PVP and HPMC at 60 °C and 0%RH.

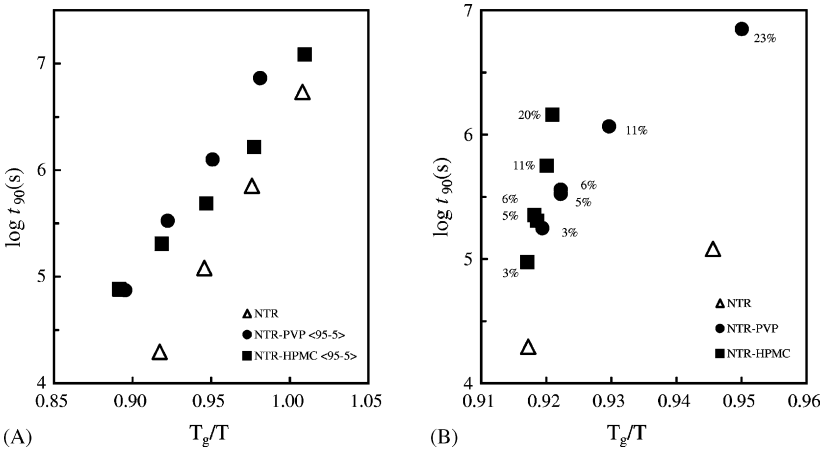

Fig. 7. Relationship between T_g/T and t_{90} of crystallization for NTR in the pure amorphous form and solid dispersions with PVP and HPMC. Numbers in percentage terms in figure (B) denote polymer contents.

ing peak at approximately 130 °C, the crystallization of NTR in the presence of the polymers was considered to be transition into a metastable form in a similar manner as that observed for pure amorphous NTR. Fig. 6 shows the effect of polymer excipients on the t_{90} values. Both PVP and HPMC increased t_{90} as the amount of polymer increased, but PVP was more effective in stabilizing amorphous NTR within the range of content studied. Fig. 7(A) shows the temperature dependence of t_{90} for solid dispersions containing 5% polymer. The t_{90} value compared at the same T_g/T was longer for both NTR-polymer dispersions than for pure NTR. Furthermore, the t_{90} versus T_g/T plots for solid dispersions containing various amounts of polymers did not overlap with that for pure NTR (Fig. 7(B)), indicating that crystallization of NTR was inhibited by the addition of PVP and HPMC to a greater extent than expected from the increased T_g. The present results imply that the drug-polymer interaction as well as an antiplasticizing effect of polymer excipients retarded the crystallization of the amorphous solid (Hirasawa et al., 2003a,b, 2004; Aso et al., 2004; Miyazaki et al., 2004, 2006; Wang et al., 2006).

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References

Andronis, V., Zografi, G., 2000. Crystal nucleation and growth of indomethacin polymorphs from the amorphous state. J. Non-Cryst. Solids 271, 236–248.

Aso, Y., Yoshioka, S., Otsuka, T., Kojima, S., 1995. The physical stability of amorphous nifedipine determined by isothermal microcalorimetry. Chem. Pharm. Bull. 43, 300–303.

Aso, Y., Yoshioka, S., Kojima, S., 2001. Explanation of the crystallization rate of amorphous nifedipine and Phenobarbital from their molecular mobility as measured by ^{13}C nuclear magnetic resonance relaxation time and the relaxation time obtained from the heating rate dependence of the glass transition temperature. J. Pharm. Sci. 90, 798–806.

Aso, Y., Yoshioka, S., Kojima, S., 2004. Molecular mobility-based estimation of the crystallization rates of amorphous nifedipine and Phenobarbital in poly(vinylpyrrolidone) solid dispersions. J. Pharm. Sci. 93, 384–391.

Burger, A., Koller, K.T., 1996. Polymorphism and pseudopolymorphism on nifedipine. Sci. Pharm. 64, 293–301.

Burger, A., Rollinger, J.M., Brüggeller, P., 1997. Binary system of (*R*)- and (*S*)-nitrendipine—polymorphism and structure. J. Pharm. Sci. 86, 674–679.

Hancock, B.C., Zografi, G., 1997. Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. 86, 1–12.

Hirasawa, N., Ishise, S., Miyata, H., Danjo, K., 2003a. Physicochemical characterization and drug release studies of Nilvadipine solid dispersions using water-insoluble polymer as a carrier. Drug Dev. Ind. Pharm. 29, 339–344.

Hirasawa, N., Ishise, S., Miyata, H., Danjo, K., 2003b. An attempt to stabilize Nilvadipine solid dispersion by the use of ternary systems. Drug Dev. Ind. Pharm. 29, 997–1004.

Hirasawa, N., Ishise, S., Miyata, H., Danjo, K., 2004. Application of Nilvadipine solid dispersion to tablet formulation and manufacturing using crospovidone and methylcellulose as dispersion carriers. Chem. Pharm. Bull. 52, 244–247.

Hirayama, F., Honjo, M., Arima, H., Okimoto, K., Uekama, K., 2000. X-ray crystallographic characterization of Nilvadipine monohydrate and its phase transition behavior. Eur. J. Pharm. Sci. 11, 81–88.

Kuhnert-Brandstätter, M., Völlenklee, R., 1986. Beitrag zur polymorphie von arzneistoffen 2. Mitteilung: halofenat, lorcainidhydrochlorid, minoxidil, mopidamol und nitrendipin. Sci. Pharm. 54, 71–82.

Miyazaki, T., Yoshioka, S., Aso, Y., Kojima, S., 2004. Ability of polyvinylpyrrolidone and polyacrylic acid to inhibit the crystallization of amorphous acetaminophen. J. Pharm. Sci. 93, 2710–2717.

Miyazaki, T., Yoshioka, S., Aso, Y., 2006. Physical stability of amorphous acetanilide derivatives improved by polymer excipients. Chem. Pharm. Bull. 54, 1207–1210.

Ngai, K.L., Magill, J.H., Plazek, D.J., 2000. Flow, diffusion and crystallization of supercooled liquids: revisited. J. Chem. Phys. 112, 1887–1892.

Rodríguez-Hornedo, N., Murphy, D., 1999. Significance of controlling crystallization mechanisms and kinetics in pharmaceutical systems. J. Pharm. Sci. 88, 651–660.

Saleki-Gerhardt, A., Zografi, G., 1994. Non-isothermal and isothermal crystallization of sucrose from the amorphous state. Pharm. Res. 11, 1166–1173.

Wang, L., Cui, F.D., Hayase, T., Sunada, H., 2005. Preparation and evaluation of solid dispersion for Nitrendipine-carbopol and Nitrendipine-HPMCP systems using a twin screw extruder. Chem. Pharm. Bull. 53, 1240–1245.

Wang, L., Cui, F.D., Sunada, H., 2006. Preparation and evaluation of solid dispersions of Nitrendipine prepared with fine silica particles using the melt-mixing method. Chem. Pharm. Bull. 54, 37–43.

Zhou, D., Zhang, G.G.Z., Law, D., Grant, K.J.W., Schmitt, E.A., 2002. Physical stability of amorphous pharmaceuticals: importance of configurational thermodynamic quantities and molecular mobility. J. Pharm. Sci. 91, 1863–1872.