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# Differences in crystallization rate of nitrendipine enantiomers in amorphous solid dispersions with HPMC and HPMCP

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ABSTRACT

To clarify the contribution of drug–polymer interaction to the physical stability of amorphous solid dispersions, we studied the crystallization rates of nitrendipine (NTR) enantiomers with identical physicochemical properties in the presence of hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate (HPMCP) and polyvinylpyrrolidone (PVP). The overall crystallization rate at 60 °C and the nucleation rate at 50–70 °C of (+)-NTR were lower than those of (−)-NTR in the presence of 10–20% HPMC or HPMCP. In contrast, similar crystallization profiles were observed for the NTR enantiomers in solid dispersions containing PVP. The similar glass transition temperatures for solid dispersions of (−)-NTR and (+)-NTR suggested that the molecular mobility of the amorphous matrix did not differ between the enantiomers. These results indicate that the interaction between the NTR enantiomers and HPMC or HPMCP is stereoselective, and that differences in the stereoselective interaction create differences in physical stability between (−)-NTR and (+)-NTR at 50–70 °C. However, no difference in physical stability between the enantiomers was obvious at 40 °C. Loss of the difference in physical stability between the NTR enantiomers suggests that the stereoselective interaction between NTR and the polymers may not contribute significantly to the physical stabilization of amorphous NTR at 40 °C.


## 1. Introduction

Nifedipine analogues are used for treatment of cardiovascular disorders. Most of them are poorly water soluble and their bioavailability is low when administered orally in crystal form. To improve the bioavailability by increasing the dissolution rate and solubility, amorphous solid dispersions of nifedipine analogues have been studied over the past few decades (Suzuki and Sunada, 1998; Chutimaworapan et al., 2000; Vippagunta et al., 2002; Hirasawa et al., 2003a,b, 2004; Tanno et al., 2004; Karavas et al., 2005, 2006; Wang et al., 2005, 2007; Kim et al., 2006; Konno and Taylor, 2006; Huang et al., 2008; Marsac et al., 2008; Rumondor et al., 2009a,b). Drugs in an amorphous state are more easily dissolved in water than their crystalline counterparts. However, recrystallization to a thermodynamically stable form during long-term storage is a matter of concern. The physical stability of amorphous solid dispersions (crystallization tendency) has been reported to correlate with several factors, such as molecular mobility (Aso et al., 2004; Miyazaki et al., 2007), drug–excipient interactions and miscibility (Matsumoto and Zografi, 1999; Marsac et al., 2006, 2009; Miyazaki et al., 2004, 2006, 2007; Konno and Taylor, 2006; Haddadin et al., 2009; Tao et al., 2009; Telang et al., 2009). The crystallization rate of amorphous nitrendipine (NTR) increases with a decrease in the glass transition temperature ($T_g$) associated with water sorption, indicating that molecular mobility, in terms of $T_g$, is correlated with physical stability. However, amorphous nilvadipine is more stable than nifedipine, even though the two had similar $T_g$ values, indicating that the difference in physical stability between nilvadipine and nifedipine might be attributable to differences in chemical structure (Miyazaki et al., 2007). Hydrogen bond interaction between felodipine and hydroxypropylmethylcellulose (HPMC) or hydroxypropylmethylcellulose acetate succinate is considered to decrease the nucleation rate of felodipine, since no significant change in molecular mobility, reflected in $T_g$ value, has been observed (Konno and Taylor, 2006). Also, drug–excipient miscibility is reportedly related to the physical stability of nifedipines. Drug crystallization has been observed to occur earlier in solid dispersions showing phase separation due to low miscibility of the drug with the excipient polymers (Rumondor et al., 2009a,b; Marsac et al., 2010). In order to develop stable amorphous solid dispersions, it is important to clarify the relative significance of these factors for the physical stability of amorphous solid dispersions. Therefore, designing a model system that is as simple as possible is the key to evaluation of each individual factor.

NTR has an asymmetric carbon (Fig. 1), and is available as a mixture of both enantiomers. These enantiomers can be resolved by chiral chromatography. Since both enantiomers have identical physical and chemical properties, including molecular mass, $T_g$,

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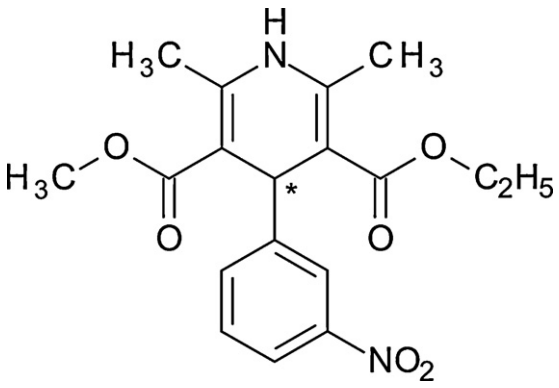


**Fig. 1.** Chemical structure of NTR. The asterisk represents asymmetric carbon.

melting point and density, the effects of molecular mobility and chemical structure on their physical stability are expected to be the same. Therefore, solid dispersions of NTR enantiomers may provide a useful model system for studies of drug–polymer stereoselective interaction. In the present study, HPMC and hydroxypropylmethylcellulose phthalate (HPMCP) were used as chiral polymers, and polyvinylpyrrolidone (PVP), an achiral polymer, was selected as a control to investigate the effect of drug–polymer interaction on the physical stability of amorphous NTR enantiomers. The overall crystallization rates were determined from the time-profiles of amorphous drug remaining, as measured by differential scanning calorimetry (DSC). Furthermore, the nucleation and the crystal growth rates of each NTR enantiomer in the solid dispersions containing HPMC, HPMCP or PVP were determined by polarized light microscopy. Measurements of $T_g$ and Fourier-transform infrared spectra (FT-IR) were carried out for evaluation of molecular mobility and drug–polymer interactions, respectively.

## 2. Materials and methods

### 2.1. Materials

PVP (PVP10) and HPMC (USP grade) were purchased from Sigma–Aldrich, Inc. HPMCP (HP-55) was kindly obtained from Shin-Etsu Chemical Co., Ltd.

NTR (Wako Pure Chemical Industries Ltd.) was resolved on a CHIRALCEL OJ-H column (Daicel Chemical Industries, Ltd., 10 mm × 250 mm) into two fractions of each enantiomer with a mobile phase of n-hexane/ethanol (100/15, flow rate: 4 ml/min). A 500 μl of 1% NTR solution in n-hexane/ethanol (1/1) was injected, and ultraviolet spectrophotometric detection was carried out at 254 nm. The circular dichroism spectrum of the first fraction exhibited a negative peak at around 360 nm, and the second one exhibited a positive peak. Therefore, the first and second fractions of NTR were designated (−)-NTR and (+)-NTR, respectively. The optical purity of each enantiomer was determined to be more than 99.96%, and the amount of photo degradation product of NTR was determined to be less than 0.03% by liquid chromatography, on a CHIRALCEL OJ-H column (Daicel Chemical Industries, Ltd.,

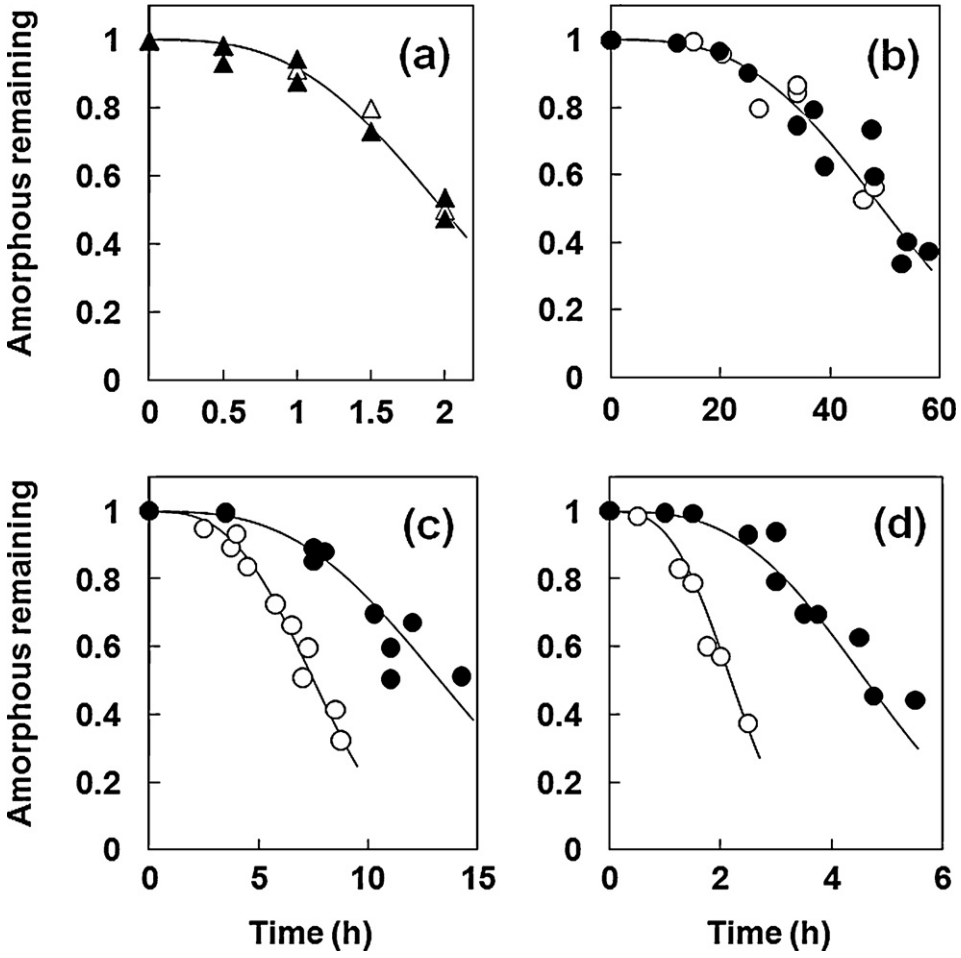


**Fig. 2.** Crystallization profiles of each NTR enantiomer alone ((a); △, ▲) and the enantiomers in solid dispersions (○, ●) with (b) 10% PVP, (c) 10% HPMC and (d) 10% HPMCP at 60 °C. Open symbols represent (−)-NTR and solid symbols represent (+)-NTR. The lines in the figures represent the best fit of the Avrami equation.