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Interplay of formulation and process methodology on the extent of nifedipine molecular dispersion in polymers☆

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ABSTRACT

The aim of this study is to evaluate effects of formulation and process technology on drug molecular dispersibility in solid dispersions (SDs). Nifedipine solid dispersions with ethylcellulose (EC) and/or Eudragit RL (RL) prepared by co-precipitation, co-evaporation, and fusion methods were characterized with FTIR, DSC, and XRPD for the content of nifedipine as molecular dispersion, amorphous and/or crystalline suspensions. A method was developed based on regular solution and Flory–Huggins theories to calculate drug–polymer interaction parameter in solid dispersion systems. A synergic effect of RL and EC on nifedipine molecular dispersibility in solid dispersions was observed. Increasing RL/EC ratio resulted in a higher degree of drug–polymer interaction that thermodynamically favored molecular dispersion, which, however, was counteracted by a corresponding decrease in the matrix glass transition point that kinetically favored phase-separation. Process methodology was found to play an important role in the formation of amorphous SD. The ranking of technologies with respect to the extent of molecular dispersion from high to low is fusion > co-evaporation > co-precipitation, wherein the solidification rate of polymeric solution and non-solvent effects were linked to kinetic entrapment of drug molecules in polymeric networks. Since nifedipine molecular dispersibility in EC/RL polymer(s) is a result of interplay between thermodynamic and kinetic factors, nifedipine molecular dispersions prepared for this study are thermodynamically metastable systems. To explore those supersaturation systems for use in drug delivery of poorly water soluble drugs, it is critical to balance drug–polymer interactions and matrix glass transition point and to consider a process technology with a fast solidification rate during formulation and process development of amorphous SD.

1. Introduction

Solid dispersion (SD) defined as "the dispersion of one or more active ingredients in an inert matrix at solid-state prepared by melting (fusion), solvent or melting–solvent method" by Chiou and Riegelman (1971) was first introduced by Sekiguchi and Obi (1961). Since then, solid dispersion-containing drug delivery systems prepared by solvent-emulsion evaporation (Barkai et al., 1990; Benita et al., 1990), hot-melting (Breitenbach, 2002; Breitenbach and Lewis, 2003), solvent evaporation (Brabander et al., 2002), co-precipitation (Huang et al., 2006a,b), spray drying (Patterson et al., 2007; Won et al., 2005), supercritical fluid (Chauhan et al., 2005), and co-grounding (Patterson et al., 2007), etc. have been reported in literature for use in improvement of bioavailability and controlled delivery of poorly water-soluble drugs. As a result of research efforts, solid dispersion dosage forms have been applied to several commercial pharmaceutical products. It is expected that with better understanding of SD molecular structure associated with its in vitro/in vivo performance (Serajuddin, 1999; Vasconcelos et al., 2007; Craig, 2002; Ford, 1986; Leuner and Dressman, 2000), there will be more SD dosage forms introduced into the market in the future. In general, it is recognized that in order to ensure optimum performance in drug dissolution and physical stability within product shelf life, ideally drug loading should be below its crystalline solubility in the SD matrix and drug is distributed within the SD at a molecular level. In practice, due to difficulties in determining drug equilibrium solubility in solid polymer (Huang and Wigent,

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2009) and high dose requirement of some therapeutic drugs, for many amorphous drug delivery systems, drug loading might be well above its crystalline solubility in the systems and the active drug might be present at a supersaturation state.

According to literature, for a supersaturated amorphous solid dispersion system, even though a fraction of drug might be present as a metastable amorphous form (Dubernet et al., 1991), it is still possible for the amorphously dispersed drug to maintain its supersaturation state throughout product shelf life by inhibiting and/or reducing drug nucleation and crystal growth rate with excipients (Vasconcelos et al., 2007). Progress has been made (Matsumoto and Zografi, 1999; Taylor and Zografi, 1997; Aso et al., 2004) in understanding stability and molecular structure of amorphous solid dispersions to a molecular level. Formation of molecular dispersion and polymeric inhibition of drug crystallization have been correlated to hydrogen-bond interaction between PVP and indomethacin (Matsumoto and Zografi, 1999). Forster et al. (2001a) observed that the differences in the physical stability of solid dispersions might be associated with interactions between drug and polymer. Significant hydrogen-bond (H-bond) interactions of nifedipine with ethylcellulose (EC) and Eudragit RL (RL) polymers were detected on solid dispersion-containing microparticles, and influences of those H-bond interactions on drug release kinetics and physical stability of molecularly dispersed drug were demonstrated (Huang et al., 2006a,b, 2008).

Considering the importance of drug molecular dispersibility on the performance of amorphous solid dispersion dosage forms, this study focused on factors that might affect the extent of molecular dispersibility of amorphous solid dispersion dosage forms, e.g., effects of formulation and process factors. The aim of this study was to investigate effects of multiple factors, namely matrix composition, drug–polymer interactions, and preparation method, on the extent of molecular dispersion, amorphous and/or crystalline suspensions. It was hypothesized that extent of drug molecular dispersion in SDs (degree of supersaturation) is a result of interplay between thermodynamic (e.g., drug–polymer interactions) and kinetic factors (e.g., solidification rate). The drug–polymer interaction could play the same role in increasing the extent of drug molecular dispersion in SDs as solute–solvent interactions in a regular solution (Martin et al., 1993; Schott, 1993), whereas kinetic factors encountered during SD preparation, such as polymer solution solidification rate (Kelley and Bueche, 1961; Bueche, 1962) and drug diffusion/partition between drug-rich and polymer-rich phases (Saylor et al., 2007, 2008), might also affect kinetic entrapment of drug molecules in the polymeric network.

In this study, nifedipine solid dispersions with various EC/RL polymer combinations prepared by three methodologies, i.e., solvent co-evaporation (slow solidification rate), fusion (fast solidification rate), and co-precipitation (slow solidification rate and with non-solvent effect), were characterized with Fourier-transformed infrared (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD). The content of molecularly dispersed nifedipine, amorphous drug present as separate domains, and crystalline nifedipine in solid dispersions at room temperature was estimated by FTIR, whereas, the amount of nifedipine solubilized in molten polymer solution at nifedipine onset melting point was determined by DSC. To assist in understanding of drug–polymer interaction and its effect on molecular dispersibility, a new method was developed from regular solution and Flory–Huggins theories (Flory, 1941; Huggins, 1941) to determine interaction parameter between drug and polymer.

2. Materials and methods

2.1. Materials

Crystalline nifedipine (Modification 1) (Burger and Koller, 1996) was purchased from Sigma (St. Louis, MO). Ethylcellulose (EC) of N7 viscosity grade (containing 0.5 unit of hydroxyl group per monomer on average) was kindly provided by Hercules (Wilmington, DE). Ammonio methacrylate copolymer, Eudragit RL®100 (RL) granules were donated by Evnoik (Piscataway, NJ). Acetone and methanol were purchased from Sigma–Aldrich (St. Louis, MO). All other materials were at least of analytical grade. Photosensitivity of nifedipine requires the storage and handling of drug samples under yellow light.

2.2. Methods

2.2.1. SD by co-precipitation method

Matrix-type microparticles containing solid dispersion of nifedipine with polymers were prepared by co-precipitation method described previously (Huang et al., 2006a). See Table 1 in Section 3 for details of the formulations. In brief, solid

Table 1
Estimation of the content of nifedipine at different physical states in solid dispersions by FTIR and DSC.

Preparation method	Polymer composition EC/RL (w/w ratio)	Drug loading (%, w/w)	FTIR method			DSC method
			Molecularly dispersed NIF content (%, w/w)	Suspended NIF content		Solubilized NIF content at onset melting point (%, w/w)
				Amorphous suspension (%, w/w)	Crystalline suspension (%, w/w)	
Co-precipitation	1/0	9.0	3.0	3.5	2.5	3.3
	2/1	16.0	5.0	5.5	5.5	9.3
	1/1	18.0	10.4	7.6	[a]	11.0
	1/2	21.0	14.4	6.6	[a]	12.8
	0/1	10.0	4.8	–	5.2	9.3
Co-evaporation	1/0	10.0	7.0	–	3.0	10
		15.0	10.7	–	4.3	14
		20.0	11.5	–	8.5	17.8
	2/1	20.0	9.6	–	10.4	16.1
	1/2	20.0	20.0	–	–	20
	0/1	10.0	10.0	–	–	10
		15.0	15.0	–	–	15
		20.0	9.1	–	10.9	19
Fusion	1/0	30.0	19.5	[b]	10.5	21.6
	0/1	30.0	30.0	–	–	30.0
		52.0	27.9	[b]	24.1	41.1

[a] Presence of crystalline nifedipine suspension was indicated by IR vibration regions at ~3332 cm^{-1}.
[b] Presence of amorphous NIF suspension was indicated by IR vibration at ~3340 cm^{-1}.

dispersion microparticles were generated by gradual addition of non-solvent (water) into an acetone solution containing nifedipine and polymer mixture. The solidified-microparticle suspension was then vacuum filtered and dried at room temperature. The dried microparticles were stored in a desiccator at room temperature and protected from light before use. The actual drug loading in the solid-dispersion microparticles was analyzed by UV–visible method (Huang et al., 2006a).

2.2.2. SD by co-evaporation method

An appropriate amount of nifedipine was dissolved in acetone solution containing EC, RL or EC/RL polymer blend at different weight ratios. Then the solvent was evaporated in an open glass beaker until a dried film was formed under room temperature. The film was removed from the glass beaker with a spatula and was gently ground with a mortar and pestle. The ground samples were stored in a desiccator at room temperature and protected from light until usage.

2.2.3. SD by fusion method

To ensure homogeneity and adequate mixing of drug with polymers, appropriate amount of nifedipine together with RL and/or EC polymer(s) was dissolved in a minimum amount of acetone in a stainless steel vessel. The solvent was then evaporated in the open vessel until a dried film was formed under room temperature. With nitrogen blanketing over the mixture inside the vessel, the dried mixture was heated on a hot plate with temperature controlled at ~176 °C by a thermostat. After the mixture was melted, the vessel was removed from the heat and quenched in an ice water for fast solidification of the co-melt. After solidification, the co-melt SD was gently ground with a mortar and pestle and the samples were stored in a desiccator at room temperature and protected from light until usage.

2.2.4. X-ray powder diffraction

X-ray powder diffraction (XRPD) was carried out with a Philips X'Pert powder diffractometer. A CuKα source operation (40 kV, 50 mA) was employed. The diffraction patterns were recorded over a 2θ angular range of 2–40° with a step size of 0.02° in 2θ and a 6 s counting per step at room temperature.

2.2.5. Differential scanning calorimetry

Differential scanning calorimetry (DSC) thermal analysis was carried out using a TA instrument (Model: DSC 2910, TA Instruments Inc., DE). The instrument was calibrated with indium. At a heating rate of 10 °C/min, samples were heated from room temperature to 200 °C in an open aluminum pan under a 10 mL/min stream of nitrogen purge. Universal Analysis (Version 2.5) software was used for analysis. The amount of nifedipine solubilized in polymer solution at on-set melting temperature of nifedipine was estimated based on heat of fusion of SD and pure crystalline nifedipine (Ma and McHugh, 2007).

$$\text{Crystalline content}\ \ (\%, \text{w/w}) = \frac{100\% \times \Delta H_{SD}}{\Delta H_{\text{pure drug}}} = \frac{100\% \times \Delta H}{115\,\text{J/g}} \quad (1)$$

$$\text{Content of solubilized drug at onset } T_m = \text{drug loading} - \text{crystalline content} \quad (2)$$

$$\text{Apparent solubility in molten polymer at onset } T_m = \frac{\text{solubilized drug content}}{100\% - \text{crystalline content}} \times 100\% \quad (3)$$

2.2.6. FT-infrared

The Fourier-transformed infrared (FTIR) spectra of samples were obtained, using an FTIR spectrophotometer (Nicollet Magna 560, Nicollet Instrument, WI, with a spectra resolution of 1 cm^{-1}). The samples were mixed with dried potassium bromide and compressed to form a KBr disc. The samples were scanned 64 times from 400 to 4000 cm^{-1}. Using a base-line adjusted peak high method (Lacoulonche et al., 1998; Yuasa et al., 1994; Kai et al., 1964), the content of nifedipine at different physical states at room temperature was estimated from the IR absorption peak height of nifedipine ester carbonyl group [molecular dispersion (~1706 cm^{-1}, peak A), phase-separated amorphous suspension (~1701 cm^{-1}, peak B), and crystalline suspension (~1689/79 cm^{-1}), peak C]. Nifedipine ester carbonyl group was chosen over its amine group because of its strong and sharp absorption peak. The content (%, w/w) of nifedipine at each physical state can be calculated as:

$$\text{Fraction at each physical state} = \frac{\text{height of a peak}}{\sum(\text{height of peak A} + \text{B} + \text{C})}$$

$$\text{Weight content}\ \ (\%, \text{w/w}) = \text{fraction at each physical state} \times \text{drug loading} \quad (4)$$

Note:

a. For convenience, the FTIR spectra presented in this paper use the traditional "% transmittance" as the *Y* axis. The fraction of nifedipine at each physical state was calculated using the absorption value [absorption value = log(100/% transmittance)].
b. For nifedipine solid dispersion with RL, due to overlapping of the non hydrogen-bonded nifedipine ester carbonyl peak (~1728 cm^{-1}) (Huang et al., 2008) (resulting from breakage of self-associated H-bonds among nifedipine molecules) with RL free ester carbonyl group at ~1736 cm^{-1}, the fraction of nifedipine that was hydrogen-bonded with RL (molecularly dispersed) cannot be directly quantified. Based on 1:1 stoichiometry mole ratio of hydrogen-bond interaction between nifedipine amine and RL carbonyl groups and similar molar extinction coefficient of functional groups in a like chemical class (Cross and Rolfe, 1951), i.e., ester carbonyl group from nifedipine and RL polymer, the amount of molecularly dispersed nifedipine was estimated from the absorption peak height of hydrogen-bonded RL ester carbonyl group at ~1706 cm^{-1}.

2.2.7. Determination of drug–polymer interaction parameters

The non-polar interaction parameter between drug and polymer, mainly attributed to drug–polymer hydrophobic interactions, is determined as

$$\chi_{1,2} = \frac{(\delta_1 - \delta_2)^2 V_2}{RT} \quad (5)$$

where *T* and *R* are absolute temperature of the samples, and gas constant, respectively. δ_1 and δ_2 are the Hildebrand solubility parameters of polymer and drug [defined as square root of cohesive energy density of the pure material: $\delta_{\text{NIFEDIPINE}} = 21.9$ (Squillante et al., 1997), $\delta_{EC} = 19.3$ (Robinson, 1989), $\delta_{RL} = 21.2$ (Minghetti et al., 1999)]. V_2 is a molar volume of nifedipine (254 cm^3/mol calculated based on true density of 1.36 g/mL (Forster et al., 2001b) and molecular weight of 346 g/mol of amorphous nifedipine).

Drug–polymer interaction parameter, including non-polar and specific interactions, was determined using a model developed by coupling regular solution and Flory–Huggins theories. Drug solid solubility in molten polymer at the onset melting point of nifedipine was estimated with DSC (Table 2), and drug–polymer interaction parameter was calculated using Eq. (11). This coupling

Table 2
Comparison of drug–polymer interactions between nifedipine–Eudragit RL® and nifedipine–ethylcellulose.

	Solid solubility in molten polymer solution at on-set melting point of NIF (%, w/w)	Solubility parameter ($MPa^{1/2}$)	Calculated non-polar interaction parameter ($\chi_{non\text{-}polar}$)	Calculated Flory–Huggins interaction parameter (χ_{FH})	Calculated specific interaction parameter ($\chi_{FH} - \chi_{non\text{-}polar}$)
Nifedipine	–	21.9[b]	–	–	–
EC	23.6[a]	19.3[c]	0.75	0.5	−0.25[e]
RL	46.1[a]	21.2[d]	0.044	−1.2	−1.24[e]

[a] Calculated with Eq. (3) using DSC data from NIF solid dispersions with RL (52%) or EC (30%) prepared by fusion method (Table 1).
[b] Squillante et al. (1997).
[c] Robinson (1989).
[d] Minghetti et al. (1999).
[e] Calculated by χ_{FH} minus $\chi_{non\text{-}polar}$.

approach has been successfully used to model solute solubility in supercritical fluid system (Kramer and Thodos, 1988). This approach was applied to the pharmaceutical SD systems of the current study. This model accounts for drug–polymer interactions including non-polar and specific interactions, solute–solvent size disparity, and excess entropy of mixing.

According to solution theory (Prausnitz, 1969), for a binary solid solute and solvent system, when the solubility of solvent in solid solute is negligible, the activity of solid solute (2) in the solvent (1) at equilibrium state can be given by

$$a_2 = \left(\frac{f^s}{f^l}\right)_{\text{pure,s}} \tag{6}$$

where a_2 represents the activity of solute in the solvent, f^s and f^l are the fugacity of the pure solute in the solid phase and liquid phase, respectively. The ratio of the fugacity at a temperature near the melting point of pure solute can be approximated (Martin et al., 1993; Kramer and Thodos, 1988; Prausnitz, 1969) by Eq. (7):

$$\ln\frac{f^s}{f^l} \cong \frac{\Delta H_2{}^{\text{fusion}}}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) = \ln a_2 \tag{7}$$

where $\Delta H_2{}^{\text{fusion}}$ is the molar heat of fusion (J/mol), R is the gas constant, T is the absolute temperature, and T_m is the melting point of the solute.

According to Flory–Huggins theory, for a binary solution of a larger molecule (component 1, assumed to be the solvent) and a small molecule (component 2, assumed to be the solute), the activity of component 2 (a_2) (Schott, 1993; Flory, 1953; Fornasiero et al., 2002) is

$$\ln\ a_2 = \ln(\phi_2) + \left(1 - \frac{r_2}{r_1}\right)(1-\phi_2) + \chi_{2,1}(1-\phi_2)^2 \tag{8}$$

where r_1 and r_2 represent the number of segments in polymer (component 1) and solute (component 2), respectively; $\chi_{2,1}$ is the Flory–Huggins interaction parameter and ϕ_2 represents the volume fraction of solute as defined by

$$\phi_2 = \frac{n_2 r_2}{n_1 r_1 + n_2 r_2} \tag{9}$$

where n_1 and n_2 are the number of molecules for polymer and solute.

The volume fraction of the solute can be estimated from the weight fraction (w_1 and w_2) and the true density (ρ_1 and ρ_2) of each component.

$$\phi_2 = \frac{w_2/\rho_2}{w_2/\rho_2 + w_1/\rho_1} \tag{10}$$

The interaction parameter ($\chi_{2,1}$) can be solved by coupling the activity derived from regular solution theory (Eq. (7)) with that from Flory–Huggins lattice theory (Eq. (8)):

$$\frac{\Delta H_2{}^{\text{fusion}}}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) = \ln(\phi_2) + \left(1 - \frac{r_2}{r_1}\right)(1-\phi_2) + \chi_{2,1}(1-\phi_2)^2$$

$$\chi_{2,1} = \frac{(\Delta H_2{}^{\text{fusion}}/R)((1/T_m) - (1/T)) - \ln(\phi_2) - (1-(r_2/r_1))(1-\phi_2)}{(1-\phi_2)^2}$$

If assuming $r_2 \ll r_1$,

$$\chi_{2,1} = \frac{(\Delta H_2{}^{\text{fuse}}/R)((1/T_m) - (1/T)) - \ln(\phi_2) - (1-\phi_2)}{(1-\phi_2)^2} \tag{11}$$

The interaction parameter calculation (Eq. (11)) used the following parameters: the true density value of drug and polymer [$\rho_1 = 1.13\ g/cm^3$ for EC and $0.83\ g/cm^3$ for RL (Rowe et al., 2003) and $\rho_2 = 1.36\ g/cm^3$ for nifedipine (Forster et al., 2001b)]; the drug solid solubility in the molten polymer (w_2) at the nifedipine onset melting temperature (T) determined from nifedipine solid dispersions with RL or EC prepared by fusion method by DSC method (Table 2); and the experimental heat of fusion of pure nifedipine ($\Delta H_2 = 115\ J/g$) at its melting temperature of $T_m = 175\ ^\circ C$. A $\chi_{2,1}$ value of 0.5 or less would indicate miscibility between drug and polymer, and a negative $\chi_{2,1}$ value would suggest a high degree of specific interactions between drug and polymer, e.g., hydrogen bonding between drug and polymer (Lacoulonche et al., 1998).

3. Results

In literature, drug is envisioned to exist or coexist in three physical states in solid dispersion formulations: molecular dispersion (drug distributed in matrix at the molecular level), amorphous suspension (phase-separated amorphous dispersion, where drug is present as discrete, drug rich domains), and crystalline suspension (Huang et al., 2006a, 2008; Dubernet et al., 1991; Appel et al., 2004). To differentiate molecularly dispersed nifedipine from amorphously suspended (phase-separated) one and to quantify the content of nifedipine at different physical states, SDs prepared for this study were analyzed using FTIR spectroscopy at room temperature. FTIR has been previously used to study interactions between drug and polymers and to identify changes in nifedipine physical state (Huang et al., 2008) as a result of changes in nifedipine hydrogen-bonding patterns after solid dispersion:

(a) the stretching vibration peaks at ~3366 cm^{-1} and ~1706 cm^{-1} were attributed to molecularly dispersed nifedipine that formed hydrogen bonds with polymers through its amine and ester carbonyl groups, respectively;
(b) the stretching vibration wavenumbers of phase-separated amorphous nifedipine were identified to be ~3346 cm^{-1} and ~1701 cm^{-1} for nifedipine amine and ester carbonyl groups (Burger and Koller, 1996), respectively;
(c) the stretching vibration peaks with wavenumbers at ~3332 cm^{-1} and ~1689/79 cm^{-1} were attributed to amine and ester carbonyl groups of crystalline nifedipine, respectively.

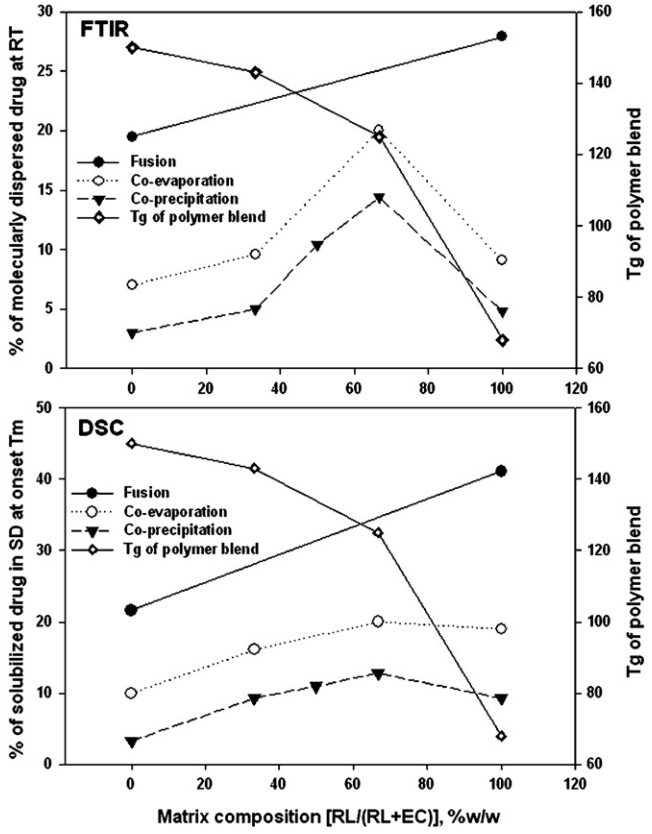

Fig. 1. Effect of polymer composition and preparation method on the extent of nifedipine molecular dispersibility (determined by FTIR) and apparent solid solubility (determined by DSC) in solid dispersions. EC – ethylcellulose, RL – Eudragit® RL polymer.

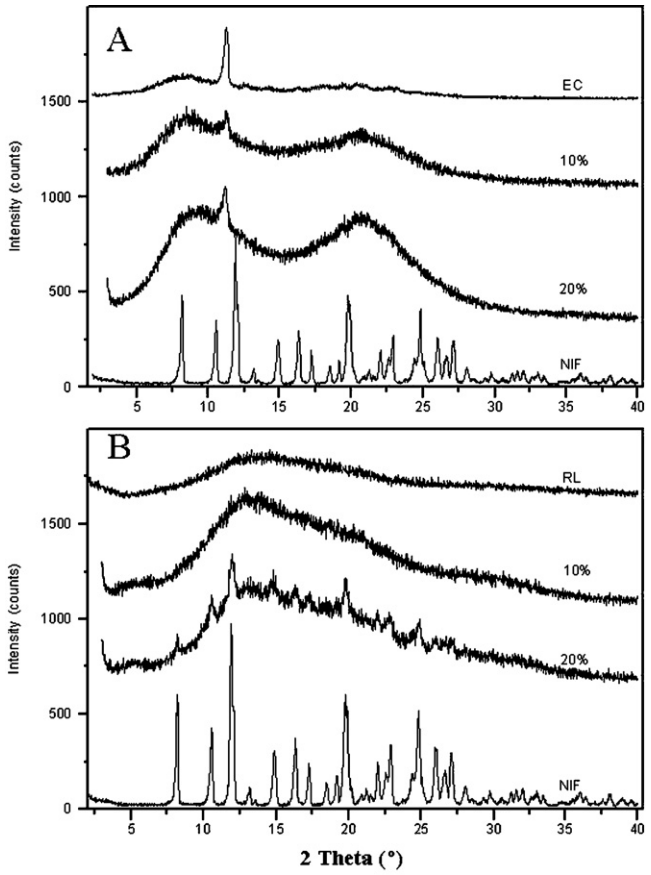

Fig. 2. X-ray diffractograms of nifedipine solid dispersions with different drug loadings prepared with co-evaporation method. (A) EC polymer; (B) RL polymer. EC – ethylcellulose powder, RLPO – Eudragit® RL polymer powder, NIF – crystalline nifedipine.

3.1. Solid dispersions prepared by co-precipitation method

Microparticles comprising solid dispersion of nifedipine with EC and/or RL polymer(s) prepared by co-precipitation method have been previously evaluated for solid-state properties, micromeritics, release kinetics, physical stability, and drug–polymer interactions (Huang et al., 2006a,b, 2008). Previous XRPD studies indicated that combination of EC and RL polymer would enhance amorphous drug loading in solid dispersions. The SD prepared at the ratio of EC/RL = 1/2 could load ~21% (w/w) of amorphous nifedipine, whereas the SDs prepared using a single polymer, namely EC and RL, could load less than 10% of amorphous nifedipine in those SDs. Further analysis of FTIR data of those SDs (Huang et al., 2006a,b, 2008) indicated that combination of EC and RL polymer could also enhance the extent of molecular dispersion. The highest extent of molecular dispersion of nifedipine in each formulation was estimated by FTIR to be 3.0%, 5.0%, 10.4%, 14.4% and 4.8% for those SDs with EC/RL = 1/0, 2/1, 1/1, 1/2, 0/1 (w/w), respectively (Table 1 and Fig. 1). A similar trend in the amount of nifedipine solubilized in molten polymer solutions at nifedipine onset melting point as a function of EC/RL ratio was also observed with the DSC data (Table 1 and Fig. 1).

3.2. Solid dispersions prepared by solvent co-evaporation method

Based on the study results of microparticles prepared by co-precipitation method, it appeared that the ratio of RL to EC polymer influenced molecular dispersibility of nifedipine in solid dispersions. However, since co-precipitation is a process involving co-precipitation of drug and polymer in the presence of solvent and non-solvent, it would be of great interest to further assess effects of polymer(s) on nifedipine molecular dispersibility under a slow solidification rate and in the absence of non-solvent effect. Under this method, with gradual evaporation of solvent at room temperature, drug–polymer solution was solidified slowly to form solid dispersions.

For solid dispersion of nifedipine with EC, diffraction peaks attributed to crystalline nifedipine were not detected by XRPD at 20% (w/w) of drug loading level (Fig. 2A). However, further examination of nifedipine physical state by FTIR (Fig. 3A) suggested that nifedipine molecular dispersion (~1706 cm^{-1}) and crystalline suspension (~1689 cm^{-1}, shown as shoulder) coexisted at that drug loading level. Probably due to sensitivity of the instrument (Shah et al., 2006; Yu, 2001), nifedipine microcrystalline particles evaded the detection by XRPD. Nifedipine present as a separated amorphous phase was not detected by FTIR in those SDs. Confirming the FTIR observations, a very weak endothermic melting transition of crystalline nifedipine in the SD prepared at 10% (w/w) drug loading started to appear in DSC thermograms (Fig. 4A). As the nifedipine loading was increased to 15% (w/w) and up, an endothermic peak attributed to melting transition of nifedipine crystals was clearly shown at ~167 °C.

For nifedipine solid dispersion with RL polymer, XRPD diffractograms (Fig. 2B) indicated that more than 10% but less than 20% of amorphous nifedipine could be incorporated into RL polymer by the co-evaporation method. Further examination of nifedipine physical state by FTIR (Fig. 3B) indicated that nifedipine was molecularly dispersed in RL at 15% of drug loading. No phase-separated amorphous nifedipine was detected in those SDs. Interestingly,

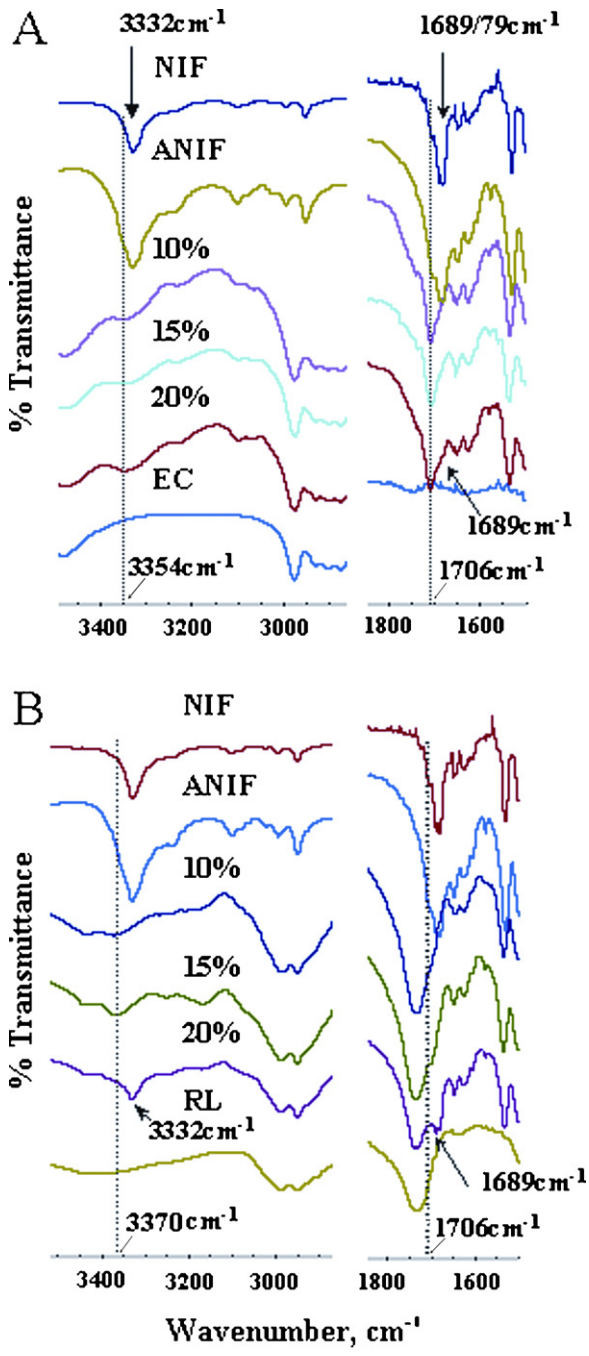

Fig. 3. FTIR spectra of nifedipine solid dispersions with different drug loadings prepared with co-evaporation method. (A) EC polymer; (B) RL polymer. EC – ethylcellulose, RL – Eudragit® RL polymer, NIF – crystalline nifedipine, ANIF – amorphous nifedipine. Dotted lines indicate stretch vibration wavenumber of ester carbonyl (~1706 cm^{-1}) and amine group (~3354 cm^{-1} for EC solid dispersion and ~3370 cm^{-1} for RL solid dispersion) of molecularly dispersed nifedipine, respectively. Arrows (←) point to stretching vibration of ester carbonyl (~1689 cm^{-1}) and amine (~3332 cm^{-1}) groups of crystalline nifedipine, respectively.

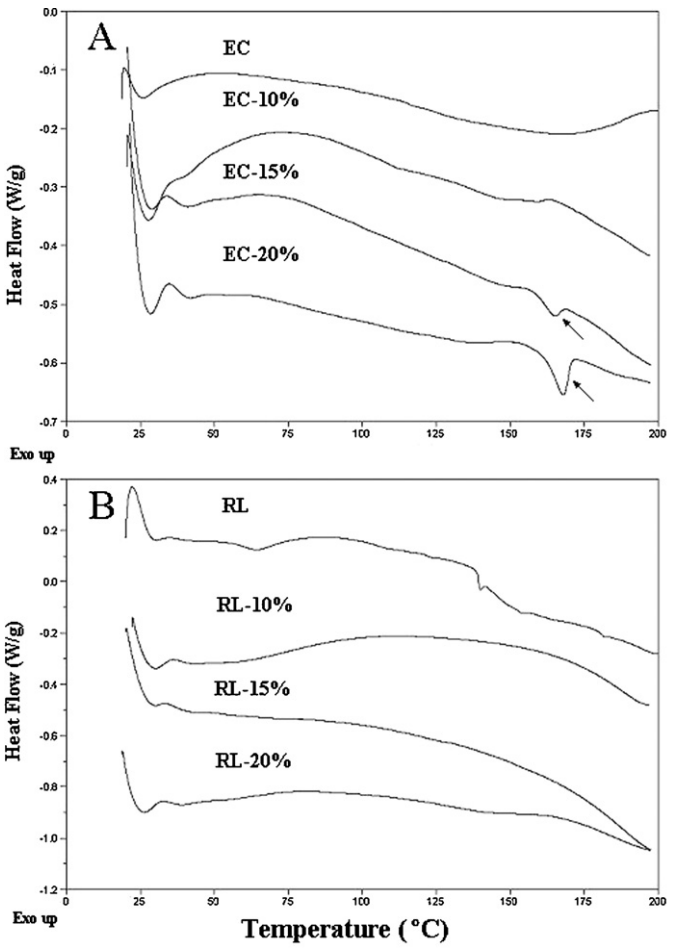

Fig. 4. DSC thermograms of solid dispersions of different drug loadings prepared with co-evaporation method. (A) EC polymer; (B) RL polymer. EC – ethylcellulose, RL – Eudragit® RL polymer. Arrows (←) indicated the melting transition of crystalline nifedipine.

despite of nifedipine crystallinity observed at 20% of drug loading, the endothermic melting peak of crystalline nifedipine in the DSC thermograms was diffusive and majority of nifedipine crystalline was dissolved prior to its onset melting point at ~138 °C (Fig. 4B); After the solid dispersion was melted and cooled down to room temperature, a clear RL polymer film was obtained; and no re-crystallization of nifedipine was observed by polarized light microscopy and FTIR spectroscopy (results not shown). Similar findings with respect to dissolution of drug in polymer prior to its onset melting point during DSC heating process have been reported for other solid dispersions (Vippagunta et al., 2002). These findings suggested that nifedipine crystalline solubility in RL polymer is temperature dependent; during DSC heat process, nifedipine was progressively solubilized into the RL polymer before reaching its onset melting point.

Similar to those solid dispersions prepared by co-precipitation method, a synergic effect of EC and RL on the extent of nifedipine molecular dispersion was also observed (Fig. 1). The highest extent of molecular dispersion was also found at EC/RL ratio of 1/2 (w/w). A similar trend in the amount of nifedipine solubilized in molten polymer solutions at NIF onset melting temperature was observed with the DSC data (Fig. 1).

3.3. Solid dispersion prepared by fusion method

Based on the findings of solid dispersions made by co-evaporation method, further studies were conducted to investigate molecular dispersibility of nifedipine in RL and EC polymer in solid dispersions prepared with fusion method. To ensure intimate mixing of drug with polymers and equilibrium between drug and polymer, drug and polymer mixture was pre-dissolved in a solvent. After solvent evaporation and drying, the mixture was fused and then quenched down to solidify the co-melt at a fast rate.

For EC solid dispersion with 30% of nifedipine loading, saturation of the polymer matrix with nifedipine was clearly indicated by

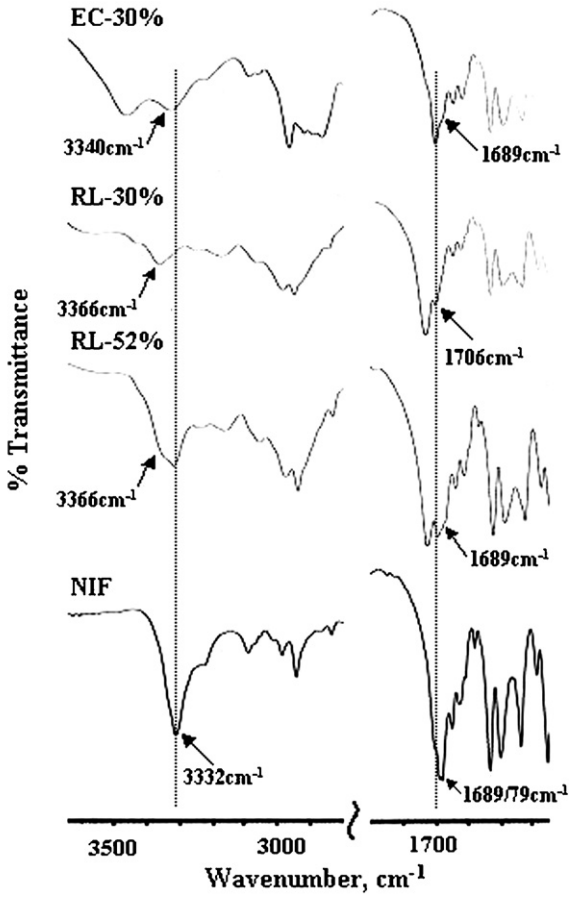

Fig. 5. FTIR spectra of nifedipine solid dispersions of different drug loadings prepared with fusion method. EC – ethylcellulose, RL – Eudragit® RL polymer, NIF – crystalline nifedipine. Dotted lines indicate stretch vibration wavenumber of ester carbonyl group from molecularly dispersed nifedipine (~1706 cm^{-1}), and stretch vibration wavenumber of amine group (~3332 cm^{-1}) from crystalline nifedipine.

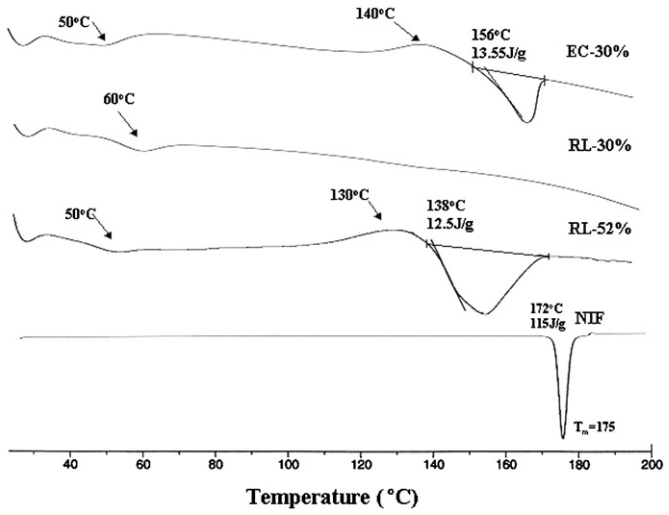

Fig. 6. DSC thermograms of nifedipine solid dispersions of different drug loadings prepared with fusion method. EC – ethylcellulose, RL – Eudragit® RL polymer, NIF – crystalline nifedipine.

coexistence of FTIR stretching vibration peaks of molecularly dispersed (1706 cm^{-1}) and crystalline (1689 cm^{-1}, shown as shoulder) nifedipine (Fig. 5). Majority of nifedipine was molecularly dispersed within EC (~19.5% of total SD weight), however, there was approximately 10.5% (w/w) of nifedipine present as crystalline nifedipine suspension. Trace of phase-separated amorphous nifedipine present in the SD was also indicated by broad nifedipine amine vibration peak at ~3340 cm^{-1} (Fig. 5) and by its glass transition at ~50 °C in DSC thermograms (Fig. 6). An exothermic transition peak attributed to recrystallization of metastable amorphous nifedipine (~140 °C) as well as an endothermic peak attributed to the melting transition of nifedipine crystals (onset melting point: ~156 °C) were observed in the DSC thermograms. The content of nifedipine solubilized in the molten EC polymer at the onset melting point of nifedipine was estimated to be 21.6% by DSC.

For nifedipine solid dispersions with RL prepared by the fusion method, only the stretching vibration peaks attributed to the amine (~3366 cm^{-1}) and ester carbonyl (~1706 cm^{-1}) groups of molecularly dispersed nifedipine were detected at 30% of drug loading (Fig. 5). When drug loading was further increased to 52% (w/w), coexistence of stretching vibration peaks, attributed to the molecularly dispersed nifedipine (~1706 cm^{-1} and ~3366 cm^{-1} for ester carbonyl and amine group, respectively) and crystalline nifedipine (~1689 cm^{-1} and ~3332 cm^{-1} for ester carbonyl and amine groups, respectively), clearly indicated saturation of the polymer matrix with nifedipine. The content of nifedipine dispersed at a molecular level at room temperature was estimated to be 27.9% by FTIR. Correspondingly, DSC study showed no thermal transition other than the glass transition of RL polymer solution (~60 °C) for SD of RL with 30% of drug loading (Fig. 6); when drug loading was increased to 52% (w/w), coexistence of molecular-dispersed nifedipine with phase-separated amorphous and crystalline drug was also indicated by nifedipine glass transition at ~50 °C, an exothermic peak attributed to recrystallization of metastable amorphous nifedipine (~130 °C), and an endothermic peak attributed to the melting transition of nifedipine crystals (onset melting point: ~138 °C) (Fig. 6). The content of nifedipine solubilized in molten RL polymer at onset melting point of nifedipine was determined to be 41.1% (w/w) by DSC.

4. Discussion

Based on the extent of nifedipine molecular dispersion (estimated by FTIR at RT) and apparent solid solubility (determined by DSC at nifedipine onset melting point) in those SD formulations prepared for this study (Fig. 1), it appeared that RL polymer has a higher solubilization capacity for nifedipine than EC. Moreover, for solid dispersions prepared by co-precipitation and co-evaporation methods, a synergic effect of these two polymers on the extent of molecular dispersion was observed and the maximum loading of molecularly dispersed nifedipine was found at the ratio of EC/RL = 1:2 (w/w). In addition, molecular dispersibility of nifedipine in solid dispersions appeared to depend on the preparation method as well: the ranking of the extent of nifedipine molecular dispersibility in solid dispersions prepared by the different methods is fusion > co-evaporation > co-precipitation.

As indicated by drug–polymer interaction parameters ($\chi_{2,1}$) calculated from Hildebrand solubility parameter and the model developed from regular solution and Flory–Huggins theories (Table 2), the difference in the extent of nifedipine (NIF) molecular dispersion between RL and EC solid dispersion could be attributed to different degrees of drug–polymer interactions (Martin et al., 1993; Schott, 1993). The calculated interaction parameter between nifedipine and polymer based on Hildebrand solubility parameters (Hildebrand and Scott, 1950), which mainly accounts for non-polar hydrophobic interactions, indicated that nifedipine–RL ($\chi_{2,1}$ = 0.044) had a higher degree of non-polar interactions than that of NIF–EC ($\chi_{2,1}$ = 0.75) (Table 2). Furthermore, a higher degree of specific interactions between NIF–RL than that of NIF–EC was also indicated by the interaction parameter associated with

specific interactions between nifedipine and RL ($\chi_{2,1} = -1.2$) and EC ($\chi_{2,1} = -0.25$). Since the magnitude of specific interaction energy is higher than other non-polar interaction forces, the main thermodynamic factors influencing drug molecular dispersibility in polymers might come from the drug–polymer specific interactions, e.g., hydrogen-bond interactions between nifedipine and polymers for this study (Langer et al., 2003). EC monomer (MW = 237 Da) has ~0.5 units of hydroxyl group available for hydrogen bonding, whereas RL has 1 unit of carbonyl group per monomer (MW = 107 Da); this difference in availability of hydrogen-bond interaction sites per mass of polymer might cause a different degree of specific interaction between nifedipine and the polymers (Lacoulonche et al., 1998; Yuasa et al., 1994; Huang and Deanin, 2004). In addition, a higher flexibility of RL polymer chain than EC might also help in movement and rotation of polymer to form linear orientation required to form hydrogen bonds (Yuasa et al., 1994).

The synergic effect of EC and RL polymer on nifedipine molecular dispersibility in solid dispersions prepared by solvent co-precipitation and co-evaporation methods was attributed to interplay of thermodynamic, e.g., drug–polymer interactions, and kinetic factors, e.g., solidification rate of the polymeric solution. Increasing RL/EC ratio resulted in a higher degree of drug–polymer H-bond interactions that favored molecular dispersion (Martin et al., 1993; Schott, 1993; Kotiyan and Vavia, 2001). However, due to a corresponding decrease in the glass transition point and thereafter reduced rigidity of the RL/EC binary polymer matrix (Fig. 1), the duration for polymer solution to solidify at room temperature was prolonged since a lower level of solvent volume fraction was required for solidification of polymeric solution (Kelley and Bueche, 1961; Bueche, 1962; Tsea et al., 1999). The increase in solidification duration could allow time for phase separation of the system into polymer-rich and drug-rich phases and thereafter drug recrystallization prior to solidification of the polymeric solution phase that immobilized the movement of drug molecules (Saylor et al., 2007, 2008; Ma and McHugh, 2007).

The difference in nifedipine molecular dispersibility observed on SDs prepared by different methods was mainly attributed to the kinetic factors, e.g., polymeric solution solidification rate and partition of nifedipine between drug-rich and polymer-rich domains. A lower extent of molecular dispersion of nifedipine in SD prepared by co-precipitation than that by co-evaporation method is mainly attributed to the presence of non-solvent (water) that reduces the amount of nifedipine partitioned into the polymeric solution prior to its solidification (Ma and McHugh, 2007). Whereas, a lower extent of molecular dispersibility of nifedipine in solid dispersion prepared by co-evaporation than that by fusion method is mainly attributed to a slower rate of solidification process (Chiou and Riegelman, 1971; Appel et al., 2004) that could allow time for diffusion and partition of nifedipine between drug-rich and polymer-rich phase according to diffusion-interface theory (Saylor et al., 2007, 2008; Ma and McHugh, 2007). In general, a faster solidification process (shorter duration) could generate solid dispersion of less crystallinity (Chiou and Riegelman, 1971; Appel et al., 2004) since more molecularly dispersed drug would be kinetically trapped in the polymeric network prior to matrix solidification.

5. Summary and conclusions

The key findings of the study showed that since drug molecular dispersibility in solid dispersion is a result of interplay between thermodynamic and kinetic factors, nifedipine molecular dispersions prepared by fusion, co-evaporation and co-precipitation methods in this study are thermodynamically metastable systems.

- In a binary system, nifedipine has higher level of molecular dispersibility in RL polymer than EC polymer.
- Interaction parameters calculated from solubility parameter and Flory–Huggins theories support that higher level of dispersibility of nifedipine in RL compared to EC could be partially attributed to higher degree of drug–polymer interactions (thermodynamic factor).
- Higher molecular dispersibility of nifedipine was achieved in the ternary systems (polymer blend) than that in the binary systems (pure polymer). The synergic effect of polymer blend on nifedipine molecular dispersibility in the ternary system was attributed to balanced effects from drug–polymer interactions (thermodynamic factor) imparted mainly by the RL component and matrix rigidity (related to glass transition point) imparted mainly by EC (kinetic factor).
- Furthermore, the difference in molecular dispersibility observed with different process methodologies is primarily related to kinetic factors; a process achieving fast solidification (kinetic factor) of the polymeric solution phase has a potential of achieving a higher fraction of molecularly dispersed drug. Although those amorphous systems might be thermodynamically metastable, they still could be explored to achieve a high amorphous drug loading by maintaining kinetic stability within product shelf time with judicious choice of formulation and storage conditions. The ranking of process methodology that generated a higher degree of supersaturation is fusion > co-evaporation > co-precipitation.

Based on the study results, it is recommended that in order to achieve a high extent of molecular dispersion, a polymer or a polymer mixture balancing drug–polymer interactions (solubilization) and glass transition point of the system, a process with a fast solidification rate, and their combinations be considered for formulation/process development of amorphous solid dispersions. The stability of those amorphous solid dispersion also has to be evaluated, which will be an interesting topic of another investigation.

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