European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 493–499

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine

Hajime Konno [a], Tetsurou Handa [b], David E. Alonzo [c], Lynne S. Taylor [c,*]

[a] Pharmaceutical Research and Technology Laboratories, Astellas Pharma Inc., Japan
[b] Department of Biosurface Chemistry, Kyoto University, Kyoto, Japan
[c] Department of Industrial and Physical Pharmacy, Purdue University, IN, USA

ARTICLE INFO

Article history:
Received 25 March 2008
Accepted in revised form 16 May 2008
Available online 6 June 2008

Keywords:
Solid dispersion
Amorphous
Dissolution
Concentration

ABSTRACT

Amorphous solid dispersions are used as a strategy to improve the bioavailability of poorly water-soluble compounds. When formulating with a polymer, it is important not only for the polymer to stabilize against crystallization in the solid state, but also to improve the dissolution profile through inhibiting crystallization from the supersaturated solution generated by dissolution of the amorphous material. In this study, the dissolution profiles of solid dispersions of felodipine formulated with poly(vinylpyrrolidone) (PVP), hydroxypropyl methylcellulose (HPMC) or hydroxypropyl methylcellulose acetate succinate (HPMCAS) were compared. In addition, concentration versus time profiles were evaluated for the supersaturated solutions of felodipine in the presence and absence of the polymers. HPMCAS was found to maintain the highest level of supersaturation for the greatest length of time for both the dissolution and solution crystallization experiments, whereas PVP was found to be the least effective crystallization inhibitor. All polymers appeared to reduce the crystal growth rates of felodipine at an equivalent supersaturation and this mechanism most likely contributes to the enhanced solution concentration values observed during dissolution of the amorphous solid dispersions.

1. Introduction

It is well known that utilizing the amorphous form of a drug can be a useful approach to improve the dissolution behavior and bioavailability of poorly water-soluble active pharmaceutical ingredients (API) [1–5]. However, amorphous compounds are thermodynamically unstable and may crystallize over pharmaceutically relevant timescales, negating any solubility advantage. Amorphous compounds can often be stabilized by combining the active ingredient with a carrier polymer to form an amorphous molecular level solid dispersion, as described in several comprehensive reviews [5–7]. The properties of the resultant solid dispersions are influenced by the physicochemical properties of both the active pharmaceutical ingredient and the carrier polymer.

In the solid state, the inhibitory effects of polymers against crystallization have been attributed to various mechanisms including antiplasticization by the polymers [8–10], interactions between the API and polymers in solid dispersions [11–13], a reduction in local molecular mobility due to coupling between the polymer and API motions [11,14], and an increase in the activation energy for nucleation [15].

While it is obviously critical to maintain the amorphous form in the solid state, the longevity of the supersaturation achieved during the dissolution stage is also of critical importance. The theoretical solubility of an amorphous form is often predicted to be much higher than the experimentally observed value [3]. In many instances, this discrepancy may be attributed, at least in part, to the rapid crystallization of a lower solubility form from the supersaturated solution. In dissolution studies of amorphous solid dispersions, API solution concentrations much higher than those attained with the thermodynamically stable crystal form are often observed, indicating that supersaturated solutions are being generated. Furthermore, the concentration–time profiles attained with solid dispersions may be higher than those achieved with the pure amorphous API [16] suggesting that certain polymers are able to further enhance solution concentrations relative to pure amorphous drug. The increased solution concentrations observed following dissolution of amorphous solid dispersions have been attributed to the inhibition of API crystallization from the supersaturated solution by the polymer [16,17] and increased equilibrium solubility of the API due to solution complexation with the polymer [18–20].

The purpose of this study was to compare the ability of three different polymers, poly(vinylpyrrolidone) (PVP), hydroxypro-

* Corresponding author. Department of Industrial and Physical Pharmacy, School of Pharmacy, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA. Tel.: +1 765 496 6614; fax: +1 765 494 6545.
E-mail address: ltaylor@pharmacy.purdue.edu (L.S. Taylor).

0939-6411/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2008.05.023

pylmethylcellulose (HPMC) and hydroxypropylmethylcellulose acetate succinate (HPMCAS) to improve the dissolution of a model poorly water-soluble compound, felodipine. These polymers were selected due to their widespread use in solid dispersions. In recent studies, it was found that the nucleation rate of felodipine in the amorphous solid dispersions did not vary with polymer type in the absence of moisture [21], whereas upon exposure to atmospheric moisture, the three polymers tested were found to exhibit a diversity of inhibitory effects [22]. For the latter study, the inhibitory effect of the polymer was found to correlate the both the amount of polymer and the amount of moisture in the solid dispersion. Having compared the relative ability of the three polymers to act as crystallization inhibitors in the solid state, it was of interest to examine the dissolution behavior of each solid dispersion system. The dissolution profile of the drug from the various amorphous solid dispersions was investigated and the concentration vs. time profiles generated during the dissolution experiments were compared to the concentration vs. time profiles of supersaturated drug solutions created by adding a concentrated solution of the drug to a medium containing the same polymers used to formulate the solid dispersions.

2. Materials

Felodipine was a generous gift from AstraZeneca, Södertälje, Sweden and hydroxypropylmethylcellulose acetate succinate (HPMCAS: Shin-Etsu AQOAT®, Type AS-MF) was a generous gifts from Shin-Etsu Chemical Co., Niigata, Japan. Poly(vinylpyrrolidone) K30 (PVP) was purchased from BASF Japan Ltd., Tokyo, Japan and hydroxypropylmethylcellulose USP (HPMC: Pharmacoat® type 606) was purchased from Shin-Etsu Chemical , Co,. Ltd., Niigata, Japan. Ethanol was obtained from Hayashi Pure Chemical Ind., Ltd., Osaka, Japan.

3. Methods

3.1. Preparation of amorphous solid dispersion

Solid dispersions were prepared using a solvent evaporation method. Felodipine was dissolved in ethanol, followed by the addition of the polymer. The solvent was evaporated under vacuum for 8 h and the resultant material was held at 160 °C for a few seconds to ensure that the dispersion was completely amorphous. The solid dispersions were subsequently pulverized by a sample mill (SK-M2 model, Kyoritsu Riko, Tokyo, Japan) and screened through a 30 mesh sieve. Optical microscopy and sieve analysis indicated that all the solid dispersions had similar particle sizes (mean particle size was between 150 and 200 μm diameter, $n = 50$).

The amorphous nature of the samples following treatment by the above procedure was confirmed using differential scanning calorimetry (DSC) which showed no endothermic peak at the melting point of the API. DSC experiments were carried out at a scanning rate of 10 °C min^{-1} using an EXSTAR 6000/DSC6220 systems (Seiko Instruments, Tokyo, Japan).

3.2. Dissolution study of solid dispersions

The dissolution rate of felodipine from various powdered solid dispersions was measured according to the reference paddle method described in the Japanese pharmacopeia (version 14), using a Riken dissolution tester (Miyamoto Riken, Osaka, Japan). Each sample, containing 30 mg of felodipine, was placed into 600 mL of the test fluid of pH 6.8. The composition of the test fluid was the same as that of the Simulated Intestinal Fluid TS described in the United States Pharmacopeia (version 26), except for the omission of pancreatin. The test solution was maintained at 37 °C and was stirred at 50 rpm. The concentration of felodipine in the solution was measured as a function of time, using an ultraviolet (UV) spectrometer (Agilent 8453, Agilent technologies, CA, USA) equipped with an automatic sampling system. A 70-μm filter was attached to the sampling device. All measurements were performed in triplicate.

3.3. Effect of polymer on the solubility of felodipine

The equilibrium solubility of crystalline felodipine in the test fluid of pH 6.8 was measured at 37 °C in the presence and absence of the polymers. 30 mg of crystalline felodipine were dispersed in 600 mL of test fluid at pH 6.8, in which 600 mg of polymer had been previously dissolved, and stirred at 50 rpm. After 24 h, the concentration of felodipine in the solutions was measured using a UV spectrometer (Agilent 8453, Agilent technologies, CA, USA). The solubility of felodipine in the test fluid in the absence of polymer was also evaluated. All measurements were carried out in triplicate.

3.4. Inhibitory effect of polymers on recrystallization from supersaturated solutions

The effect of the polymer on the solution concentration–time profile was also evaluated following the generation of supersaturated solutions of felodipine. Felodipine was dissolved in a small volume of solvent (ethanol or methanol). An aliquot of the concentrated felodipine solution was then added to 600 mL of the test fluid described above, in which either 90 mg or 30 mg of polymer had been previously dissolved, leading to a final polymer concentration of either 150 or 50 μg/mL. Sufficient concentrated felodipine solution was added to generate initial solution concentrations of either 50, 15 or 9.5 μg/ml. The solution was held at 37 °C and stirred at 100 rpm. The concentration of felodipine in the solution was measured as a function of time, using a UV spectrometer (Agilent 8453, Agilent technologies, CA, USA, or Cary 50, Varian Inc., Palo Alto, CA) with an automatic sampling system. For the Agilent system, a 70-μm filter was attached to the sampling device, for the Carey 50 system, spectra were preprocessed using a second derivative method to mitigate scattering effects from crystallizing particulates [23]. All measurements were carried out in triplicate.

4. Results

4.1. Effect of polymer on dissolution rate of felodipine from solid dispersions

Fig. 1 shows the dissolution profiles of felodipine from solid dispersions containing various amounts of each of the three carrier polymers. Dissolution from the majority of the solid dispersions resulted in solution concentrations that were higher than the equilibrium solubility of crystalline felodipine (0.9 μg/mL see Table 1 and [24]), indicating that supersaturated solutions were generated. However, solid dispersions containing between 10 and 50% w/w PVP did not result in solutions concentrations that exceeded the solubility of crystalline felodipine. Fig. 1 also shows that the supersaturation generated increased with the increasing polymer content in the solid dispersions for each of the polymers. Furthermore, the initial dissolution rate varied between the polymers tested with a maximum solution concentration being reached within 60 min for the PVP containing solid dispersions compared to the cellulosic solid dispersions where the maximum solution concentration was generally achieved between 180 and 240 min.

In Fig. 2, selected data from Fig. 1 have been replotted to enable a comparison between solid dispersions containing different

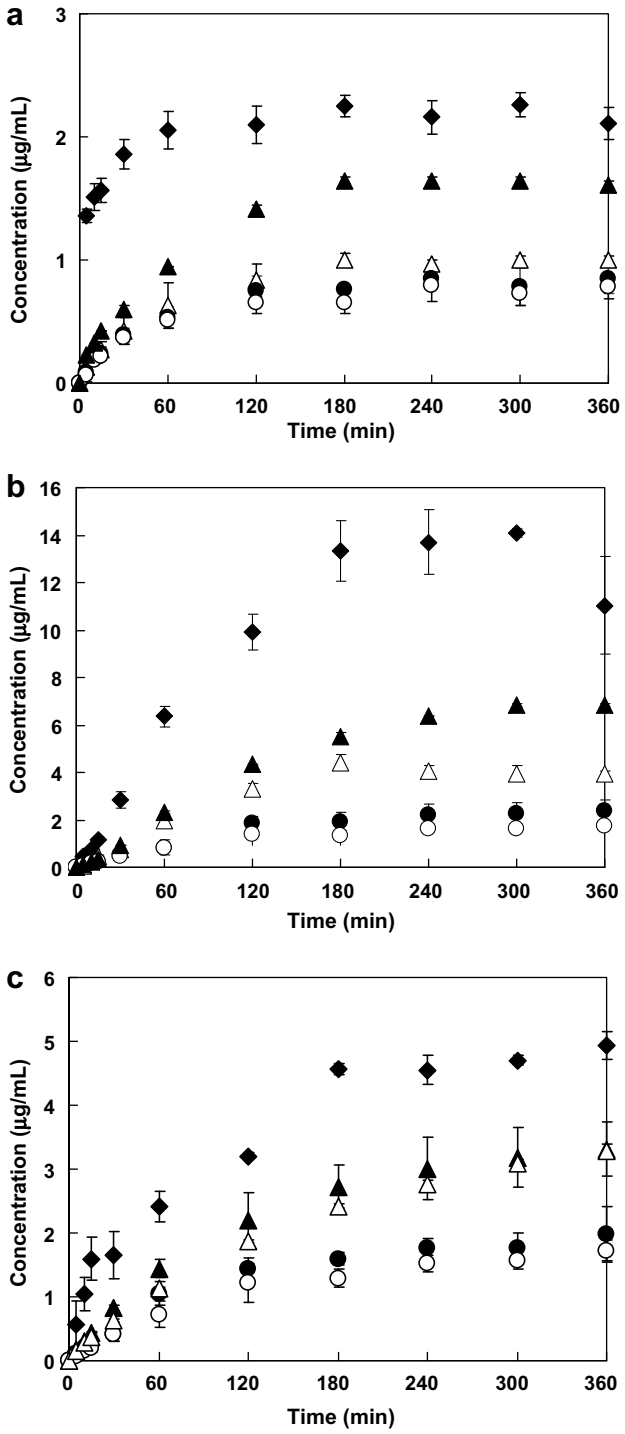

Fig. 1. Dissolution profiles of felodipine from solid dispersions with different amounts of polymers; (a) PVP, (b) HPMCAS and (c) HPMC in the test fluid of pH 6.8. Symbols represent profiles of samples with 10% (○), 20% (●), 50% (△), 60% (▲) and 75% (♦) of polymers. Error bar represents standard deviation.

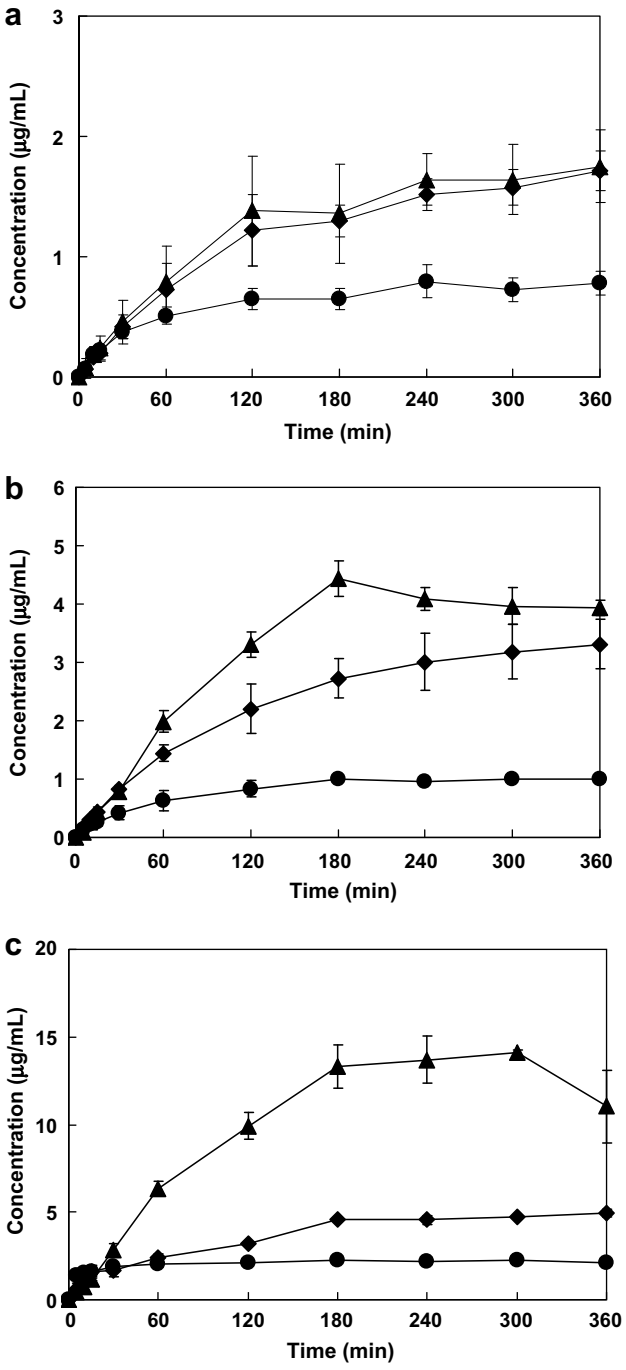

Fig. 2. Dissolution profiles of felodipine from solid dispersions with different kinds of polymers in the test fluid of pH 6.8; Solid dispersions contain (a) 10% of polymer, (b) 50% of polymer and (c) 75% of polymer. Symbols represent profiles of samples with PVP (●), HPMCAS (▲) and HPMC (♦). Error bar represents standard deviation.

Table 1
Solubility of felodipine in the test fluid pH 6.8 (JP 2nd fluid) with or without dissolved polymer at 37 °C

Added polymer	Solubility of felodipine in test fluid pH 6.8			
	Without polymer	1 mg/mL PVP	1 mg/mL HPMCAS	1 mg/mL HPMC
Solubility (μg/mL)	0.94 (0.08)	0.98 (0.09)	1.01 (0.11)	1.00 (0.10)

Values in parentheses represent the standard deviations.

polymers at the same weight fraction. As shown in Fig. 2a, there was little difference in the solution concentrations achieved with each of the polymers when the amount of polymer in the solid dispersion was only 10% w/w and the maximum solution concentrations achieved were close to the solubility of crystalline felodipine. As the amount of polymer in the solid dispersions was increased, the maximum solution concentration achieved varied considerably with polymer type, as shown in Fig. 2b and c. Dispersions containing HPMCAS resulted in the highest supersaturation while PVP was only slightly effective at improving the dissolution profile. Specifically, for solid dispersions containing 75% w/w polymer, solution concentrations of 14.1, 4.9 and 2.3 μg/mL were achieved with HPMCAS, HPMC and PVP, respectively (Fig. 2c). A more detailed view highlighting the relationship between the maximum solution concentration and the concentration of polymer in the solid dispersion is shown in Fig. 3. Here, it can be seen that for PVP, there is only a limited increase in solution concentration as a function of concentration, whereas for HPMCAS, there is a strong dependence on the amount of polymer.

The initial dissolution rates were calculated from the concentration of felodipine after 5 min of dissolution, and are shown in Fig. 4 as a function of polymer concentration. It can be seen that solid dispersions containing 75% PVP showed the highest initial dissolution rate and that the initial dissolution rate decreased with a decrease in polymer concentration in the solid dispersion.

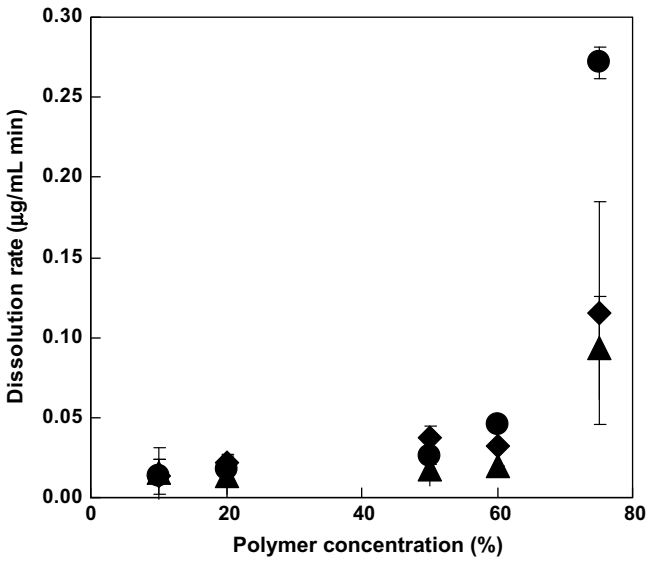

Fig. 4. Initial dissolution rate of felodipine in the test fluid calculated from the data of solubility at 5 min after suspension as a function of polymer concentration in solid dispersions. Symbol represents the type of polymer in solid dispersions; PVP (●), HPMCAS (▲) and HPMC (♦). Error bar represents standard deviation.

4.2. Inhibitory effects of the polymers on the recrystallization of felodipine from supersaturated solutions

The inhibitory effects of polymers against recrystallization of felodipine from a supersaturated solution were evaluated by adding a concentrated solution of felodipine to the test fluid in which the polymers had been dissolved and then by monitoring the solution concentration as a function of time. Fig. 5 shows results obtained at two different polymer solution concentrations, 150 μg/mL (Fig. 5a) and 50 μg/mL (Fig. 5b), which correspond to the polymer solution concentration that would be produced by total dissolution of solid dispersions containing 75% and 50% of polymer, respectively. For these experiments, the initial solution concentration of felodipine that was generated by dilution of the concentrated drug solution was 50 μg/mL. As shown in Fig. 5, in the absence of polymer, the concentration of felodipine rapidly diminishes until it reaches a value close to that of the equilibrium solubility of crystalline felodipine. For all three polymers, the initial concentration measured (5 min after the addition of felodipine) was approximately 6 μg/mL in all the cases. This solution concentration decreased only marginally over a period of 4 h when HPMC or HPMCAS was present in the solution. When present at a 50 μg/mL level, HPMC appeared to be slightly less effective at maintaining this concentration of felodipine than HPMCAS (Fig. 5b), but no difference between the two polymers was apparent at the higher polymer concentration (Fig. 5a). In contrast, the concentration of felodipine in solution decreased gradually over a 4-h period when PVP was added to the solution, eventually reaching a value close to the equilibrium solubility of felodipine. These results are qualitatively similar to those obtained previously with nifedipine [17].

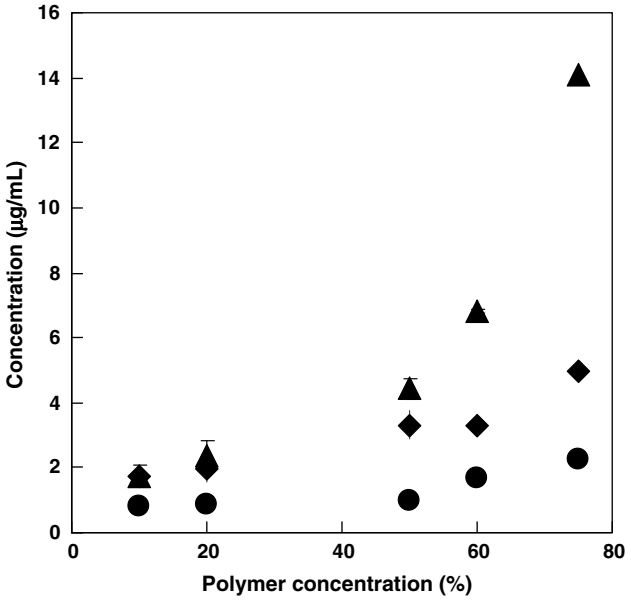

Fig. 3. Maximum solubility of felodipine in the test fluid attained during dissolution test at 0–360 min as a function of polymer concentration in solid dispersions. Symbol represents the type of polymer in solid dispersions; PVP (●), HPMCAS (▲) and HPMC (♦). Error bar represents standard deviation.

Fig. 6 shows concentration–time profiles when the initial supersaturation created was much lower than in Fig. 5, either 9.5 μg/mL (Fig. 6a) or 15 μg/mL (Fig. 6b). The polymer concentration was 150 μg/mL. For the system with an initial supersaturation of 15 μg/mL, in the presence of the cellulosic polymers, the felodipine concentration remains relatively constant at a value of approximately 11 μg/mL. For the system with an initial supersaturation of 9.5 μg/mL, the solutions containing HPMC or HPMCAS exhibited average solution concentrations between 7.8–8.9 μg/mL and 8.5–9.1 μg/mL, respectively, for the duration of the experiments. For both of these systems, the concentrations maintained during the experiments are much closer to the initial supersaturations generated and higher than for the systems shown in Fig. 5. Solutions containing PVP once again show a gradual decrease in drug concentration towards the solubility of crystalline felodipine, while for the buffer solutions, significant precipitation had occurred within 5 min of addition.

4.3. Equilibrium solubility of felodipine in the presence of the polymers

The solubility of crystalline felodipine in a solution containing 1 mg/mL of each of the three polymers was determined and compared to the solubility in a solution containing no polymer. It

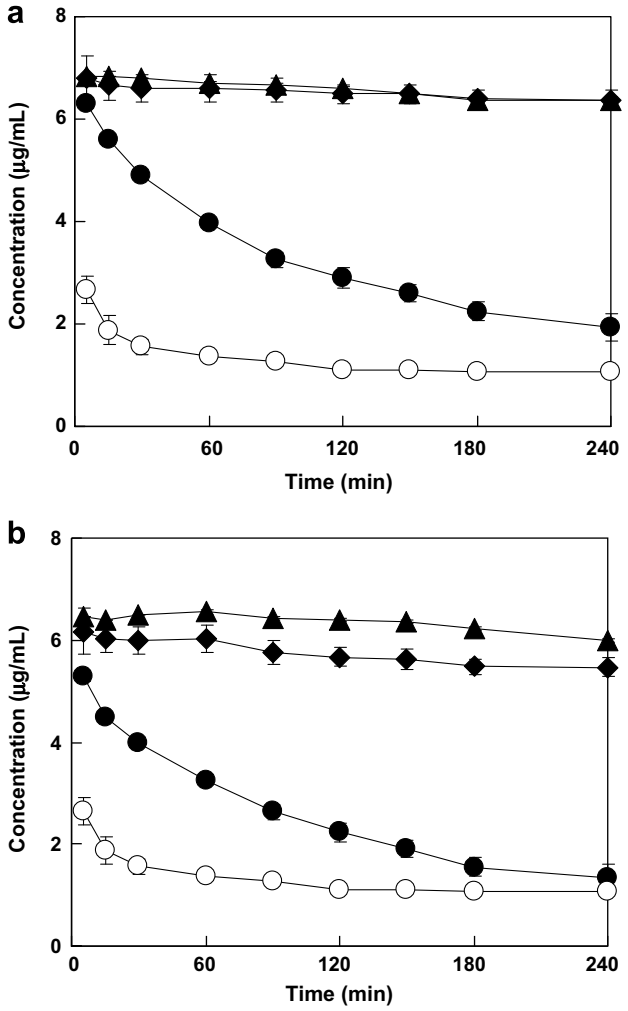

Fig. 5. Inhibitory effects of polymers on the recrystallization of a supersaturated solution of felodipine (50 μg/mL) at pH 6.8; the test fluids contain (a) 150 μg/mL of polymer, (b) 50 μg/mL of polymer. Symbols represent profiles of samples with PVP (●), HPMCAS (▲) and HPMC (♦) and in the absence of any polymer (○). Error bar represents the standard deviation, $n = 3$.

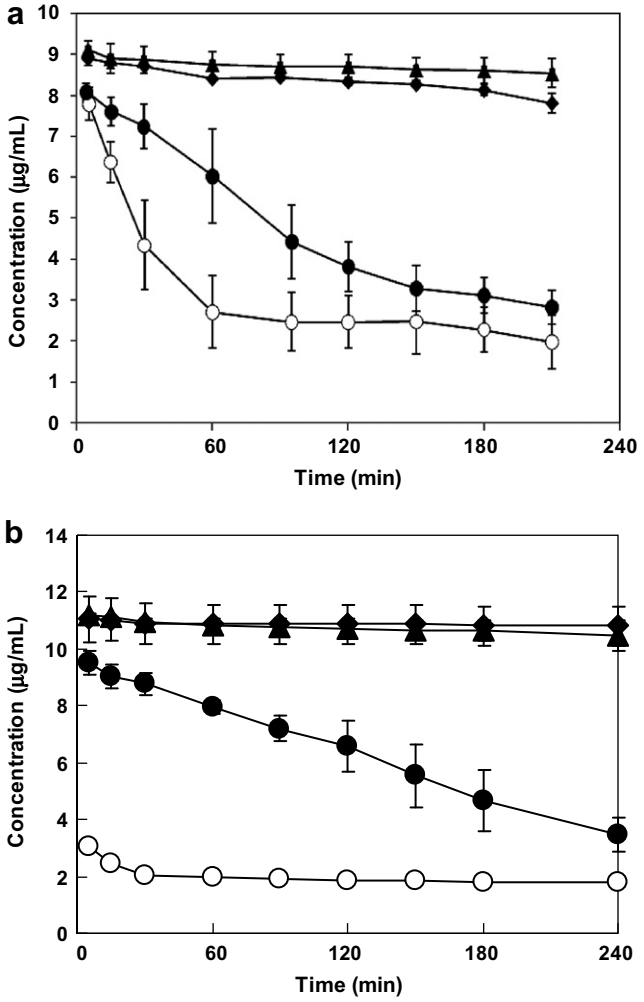

Fig. 6. Inhibitory effects of polymers on the recrystallization of supersaturated solutions of felodipine (a) initial concentration of 9.5 μg/mL and (b) initial concentration of 15 μg/mL at pH 6.8; the test fluids contain 150 μg/mL of polymer. Symbols represent profiles of samples with PVP (●), HPMCAS (▲) and HPMC (♦) and in the absence of any polymer (○).Error bar represents the standard deviation, $n = 3$.

should be noted that this polymer concentration far exceeds the solution concentrations described above. As shown in Table 1, the solubility of felodipine did not change when the polymer was present in the test fluid at this concentration. These results indicate that the observed solution concentrations of felodipine cannot be accounted for by the polymers enhancing solubility.

5. Discussion

The higher apparent solubility of amorphous materials is well known and has been extensively documented [1,3,25]. The solubility advantage arises because of disordered structure of the amorphous solid: in a crystalline material, the lattice has to be disrupted for the material to dissolve, whereas in an amorphous solid, only short range intermolecular interactions are present. The theoretical solubility ratio between the amorphous and crystalline forms at a given temperature can be approximated by Eq. (1) [3,26,27], which requires an estimation of the free energy difference between the amorphous and crystalline solids, ΔG_c,

$$\Delta G_c = RT \ln \frac{a_{\text{amorphous}}}{a_{\text{crystalline}}} \approx RT \ln \frac{S_{\text{amorphous}}}{S_{\text{crystalline}}} \quad (1)$$

where R is the gas constant, T is temperature, a is the activity and S is solubility. The Hoffman equation can be used to provide an estimate of the free energy difference between the two forms if the melting temperature (T_m) and the heat of fusion of the crystalline form are known, as shown in Eq. (2). The Hoffman equation has been found to give good estimates of the free energy difference between amorphous and crystalline felodipine [15]

$$\Delta G_c = \Delta H_f \frac{(T_m - T)T}{T_m^2} \quad (2)$$

It is clear from Eq. (2) that the higher the melting point and heat of fusion of a compound, then the greater the solubility enhancement that would be expected from utilizing the amorphous form of the drug. As pointed out by Hancock and Parks, the theoretical solubility advantage of the amorphous form is rarely achieved due to crystallization from solution [3]. Because the amorphous form dissolves to produce a solution with higher concentration than that of the crystalline solid, there is a thermodynamic driving force for crystallization. According to classical nucleation theory, the nucleation rate, J, would be expected to depend on the factors shown in Eq. (3) [28]

$$J = A \exp\left[-\frac{16\pi\gamma^3 v^2}{3k^3T^3(\ln S)}\right] \quad (3)$$

where γ is the interfacial tension, υ is the molecular volume, k is the Boltzmann constant, T is temperature, and S is supersaturation, as defined in

$$S = \frac{c}{c^*} \tag{4}$$

where c is the solution concentration and c^* is the equilibrium solubility. From Eq. (3), it is clear that the nucleation rate is strongly dependent on the degree of supersaturation that is present. Thus, it would be expected that amorphous-crystalline systems with a high theoretical solubility ratio would have a greater tendency to nucleate and precipitate from solution. Based on Eqs. (1) and (2) and the thermodynamic information tabulated by Marsac et al. [15], amorphous felodipine should yield a maximum solution concentration approximately 10 times that of the crystalline form at 37 °C, that is about 9.5 μg/mL based on the equilibrium solubility measured for crystalline felodipine (Table 1). As seen from Fig. 6, when felodipine is introduced to the system at a concentration of 9.5 μg/ml, the solution concentration decreases rapidly indicating that crystallization commences immediately. These data suggest that the dissolution of amorphous felodipine will be accompanied by rapid crystallization.

However, contrary to this prediction, as seen from Figs. 1 and 2, dissolution of amorphous felodipine intimately mixed with a polymer, in particular HPMCAS, leads to higher than equilibrium solubility solution concentrations that persist for some time. These could either arise from supersaturated solutions that have been generated by dissolution of the amorphous solid dispersion and stabilized by the polymers, and/or by an increase in the equilibrium solubility of the crystalline drug due to complexation in solution with the polymer and hence a reduced extent of supersaturation and a lowered thermodynamic driving force for crystallization [18]. Based on the solubility measurements shown in Table 1, the latter explanation can be discounted; at the concentrations used, the polymers had no influence on the solubility of crystalline felodipine. Thus it can be inferred that supersaturated solutions are generated and maintained as a result of dissolution of the solid dispersions. Support for the supposition that the polymers can stabilize the supersaturated solution is provided by Figs. 5 and 6, which show that elevated solution concentrations persist following the generation of supersaturation. Interestingly, the felodipine solution concentration in the presence of HPMC and HPMCAS decreases very slowly over a 4-h period for three different levels of supersaturation, although there is an initial immediate drop in concentration (the magnitude of this initial drop varies between systems). These results can be rationalized as follows: Creating a highly supersaturated system leads to rapid nucleation of felodipine particles and precipitation from solution. Since the nucleation rate is dependent on the concentration (Eq. (3)), the nucleation rate is expected to be higher in the more concentrated solution, leading to the creation of more particles and a more extensive initial decrease in the concentration. The polymers thus do not appear to have prevented the nucleation of felodipine under these experimental conditions. However, the observation that solution levels remain higher than the equilibrium solubility value strongly suggests that the polymers are able to inhibit crystal growth. The inhibition of crystallization and crystal growth by polymers has been observed previously [29–33]. Thus it appears that the system has decreased in concentration to a level where nucleation is no longer spontaneous (i.e. the system has moved from the labile zone into the metastable zone) and the only mechanism for a reduction in solution concentration to the equilibrium value is through crystal growth. If this process is inhibited by the polymers, then solution concentrations will presumably remain elevated above the equilibrium concentration. Overall mass growth rates (R_G) can be estimated from Eq. (5) by monitoring solution concentrations as a function of time [34]

$$R_G = \frac{1}{A_c} \times \frac{dM_c}{dt} \tag{5}$$

where A_c is the effective surface area, M_c is the mass incorporated into the crystal and t is time. If it is assumed that all four systems have similar effective surface areas, the growth rates will be directly proportional to the change in solution concentration of felodipine as a function of time. Therefore, the relative growth rates of felodipine in the presence of the various polymers can be estimated and compared. From Fig. 6a it seems that the growth rate of felodipine, where dM_c/dt has been estimated from the initial linear portion of each curve, in either buffer ($dM_c/dt \sim 0.1399$ μg/mL-min) or PVP ($dM_c/dt \sim 0.0398$ μg/mL-min) is much faster than in HPMC ($dM_c/dt \sim 0.0044$ μg/mL min) or HPMCAS ($dM_c/dt \sim 0.0021$ μg/mL min). Thus in the presence of the cellulose polymers, the slope of the concentration vs. time profile is close to zero suggesting that crystal growth is greatly inhibited (Fig. 6).

It is obviously of interest to be able to attempt to correlate the ability of a polymer to stabilize a supersaturated solution (e.g. results shown in Figs. 5 and 6), with the dissolution behavior of the corresponding solid dispersion since the former technique could be used to screen for the best polymers for a particular drug. A reasonable correlation is found for PVP and HPMCAS, where it is apparent that PVP is inferior to HPMCAS in both systems; however, results for HPMC are less predictable. In the solution experiments, HPMC is comparable to HPMCAS in terms of its ability to maintain supersaturated solutions, whereas in the solid dispersion dissolution experiments, it is not as effective as HPMCAS. Similar results were obtained by Tanno et al. for nifedipine systems [17]. At present the reasons behind these differences are not clear.

The ability of the three polymers to stabilize the supersaturated solutions generated by dissolution of the amorphous solid dispersions can be compared with the physical stability of the corresponding solid dispersions on storage in the presence and absence of moisture. While no difference was observed in the stabilizing ability of the polymers in the dry solid systems [21], HPMCAS and HPMC were superior at inhibiting crystallization relative to PVP when the solid dispersions were exposed to high relative humidities [22]. Although HPMCAS and HPMC had a similar ability to inhibit crystallization in the solid dispersions in the presence of absorbed moisture, results of this study indicate that HPMCAS generates more supersaturated solutions during dissolution of the solid dispersions. It thus appears that different crystallization inhibition mechanisms are of importance and may vary with the amount of water in the system.

6. Conclusions

The dissolution behavior of amorphous solid dispersions of felodipine prepared with PVP, HPMC and HPMCAS has been compared. Solid dispersions formulated with HPMCAS were found to result in solutions with the highest extent of supersaturation, whereas HPMC and PVP were less effective. At equivalent supersaturations, all three polymers were observed to reduce crystal growth rates relative to the growth rate of the drug alone. HPMCAS and HPMC were most effective at inhibiting growth rates while PVP was much less effective. These results indicate that it is important to select the appropriate polymer for a solid dispersion after considering both the solid state stability and the stability of the supersaturated solution generated following dissolution of the amorphous solid.

References

[1] W.L. Choiu, S. Riegelman, Oral absorption of griseofulvin in dogs: increased absorption via solid dispersion in polyethylene glycol 6000, J. Pharm. Sci. 59 (1970) 937–942.
[2] A.H. Goldberg, M. Gibaldi, J.L. Kanig, Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions, J. Pharm. Sci. 55 (1966) 487–492.
[3] B.C. Hancock, M. Parks, What is the true solubility advantage for amorphous pharmaceuticals?, Pharm Res. 17 (2000) 397–404.
[4] K. Six, G. Verreck, J. Peeters, M. Brewster, G. Van den Mooter, Increased physical stability and improved dissolution properties of itraconazole, a class II drug, by solid dispersions that combine fast- and slow-dissolving polymers, J. Pharm. Sci. 93 (2004) 124–131.
[5] C. Leuner, J. Dressman, Improving drug solubility for oral delivery using solid dispersion, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[6] W.L. Chiou, S. Riegelman, Pharmaceutical applications of solid dispersions, J. Pharm. Sci. 60 (1971) 1281–1302.
[7] A.T.M. Serajuddin, Solid dispersions of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs, J. Pharm. Sci. 88 (1999) 1058–1066.
[8] J.E. Jolley, Microstructure of photographic gelatin binders, Photogr. Sci. Eng. 14 (1970) 169–177.
[9] G. Van den Mooter, M. Wuyts, N. Blaton, R. Busson, P.GrobetP. Augustijns, R. Kinge, Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25, Eur. J. Pharm. Sci. 12 (3) (2001) 261–269.
[10] C.A. Oksanen, G. Zografi, The relationship between the glass transition temperature and water vapor absorption by poly(vinylpyrrolidone), Pharm. Res. 7 (1990) 654–657.
[11] Y. Aso, S. Yoshioka, J. Chang, G. Zografi, Effect of water on the molecular mobility of sucrose and poly(vinylpyrrolidone) in a colyophilized formulation as measured by C-13 NMR relaxation time, Chem. Pharm. Bull. 50 (6) (2002) 822–826.
[12] L.S. Taylor, G. Zografi, Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions, Pharm. Res. 14 (1997) 1691–1698.
[13] T. Miyazaki, S. Yoshioka, Y. Aso, S. Kojima, Ability of polyvinylpyrrolidone and polyacrylic acid to inhibit the crystallization of amorphous acetaminophen, J. Pham. Sci. 93 (2004) 2710–2717.
[14] Y. Aso, S. Yohioka, Molecular mobility of nifedipine-PVP and phenobarbital-PVP solid dispersions as measured by 13C NMR spin-lattice relaxation time, J. Pharm. Sci. 95 (2006) 318–325.
[15] P.J. Marsac, H. Konno, L.S. Taylor, A comparison of the physical stability of amorphous felodipine and nifedipine systems, Pharm. Res. 10 (2006) 2306–2316.
[16] P. Gupta, V.K. Kakumanu, A.K. Bansal, Stability and solubility of Celecoxib-PVP amorphous dispersions: a molecular perspective, Pharm. Res. 21 (2004) 1762–1769.
[17] F. Tanno, Y. Nishiyama, H. Kokubo, S. Obara, Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions, Drug. Dev. Ind. Pharm. 30 (2004) 9–17.
[18] F. Usui, K. Maeda, A. Kusai, K. Nishimura, K. Yamamoto, Inhibitory effects of water-soluble polymers on precipitation of RS-8359, Int. J. Pharm. 154 (1997) 59–66.
[19] F. Acartürk, O. Kislal, N. Celebi, The effect of some natural polymers on the solubility and dissolution characteristic of nifedipine, Int. J. Pharm. 85 (1992) 1–6.
[20] T. Loftsson, F. Fridriksdóttir, T.K. Gudmundsdóttir, The effect of water-soluble polymers on aqueous solubility of drugs, Int. J. Pharm. 127 (1996) 293–296.
[21] H. Konno, L.S. Taylor, Stabilizing ability of different polymers on the crystallization of molecularly dispersed amorphous felodipine, J. Pharm. Sci. 95 (2006) 2692–2705.
[22] H. Konno, L.S. Taylor, Ability of different polymers to inhibit the crystallization of amorphous felodipine in the presence of moisture, Pharm. Res. 25 (2008) 969–978.
[23] K. Bynum, K. Roinestad, A. Kassis, J. Pocreva, L. Gehrlein, F. Cheng, J. Palermo, Analytical performance of a fiber optic probe dissolution system, Dissol. Technol. 8 (4) (2001) 13–21.
[24] C. Von Corswant, P. Thorén, S. Engström, Triglyceride-based microemulsion for intravenous administration sparingly soluble substances, J. Pharm. Sci. 87 (1998) 200–208.
[25] B.C. Hancock, G. Zografi, Characteristics and significance of the amorphous state in pharmaceutical systems, J. Pharm. Sci. 86 (1997) 1–12.
[26] G.S. Parks, H.M. Huffman, F.R. Cattor, Studies on glass. II: the transition between the glassy and liquid states in the case of glucose, J. Phys. Chem. 32 (1928) 1366–1379.
[27] G.S. Parks, L.J. Snyder, F.R. Cattoir, Studies on glass. XI: some thermodynamic relations of glassy and alpha-crystalline glucose, J. Chem. Phys. 2 (1934) 595–598.
[28] D. Turnbull, J.C. Fischer, Rate of nucleation in condensed systems, J. Chem. Phys. 17 (1949) 71–73.
[29] A.P. Simonelli, S.C. Metha, W.I. Higuchi, Dissolution rates of high energy sulfathiazide-povidone coprecipitates II: characterization of form of drug controlling its dissolution rate via solubility studies, J. Pharm. Sci. 65 (1976) 355–360.
[30] T. Matsumoto, G. Zografi, Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization, Pharm. Res. 16 (1999) 1722–1728.
[31] A. Hasegawa, M. Taguchi, R. Suzuki, T. Miyata, H. Nakagawa, I. Sugimoto, Supersaturation mechanism of drugs from solid dispersions with enteric coating agents, Chem. Pharm. Bull. 36 (1988) 4941–4950.
[32] H. Suzuki, H. Sunada, Influence of water-soluble polymers on the dissolution of nifedipine solid dispersions with combined carriers, Chem. Pharm. Bull. 46 (1998) 482–487.
[33] A. Hasegawa, R. Kawamura, H. Nakagawa, I. Sugimoto, Dissolution mechanism of solid dispersions of nifedipine with enteric coating agents, J. Pharm. Sci. Technol. Jpn. 106 (1985) 586–592.
[34] J. Garside, A. Mersmann, J. Nyvlt, Measurement of crystal growth and nucleation, IChemE, second Ed., 2002, p. 15.