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Thermal Analysis and Dissolution Characteristics of Nifedipine Solid Dispersions

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ABSTRACT

Solid dispersions of nifedipine prepared with two hydrophilic carrier systems, Gelucire (44/14)/PEG 600 and PVP (K12-K25)/PEG 6000 by fusion or fusion/solvent method were characterized by thermal analysis for comparisons. Results demonstrated that both carrier systems were able to prohibit the crystallization of nifedipine after the mixture melted at a higher temperature at a ratio exceeding 50%. The extent of forming amorphous nifedipine due to the inhibition of crystallization, also raised with the increasing ratio of the carrier. When mixing with PEG 6000 at a ratio of 3 : 1, the melting temperature of nifedipine dropped to 110°C. Dissolution tests further demonstrated that nifedipine, once fused with these carriers, possessed an enhanced dissolution rate. As to the Gelucire (44/14)/PEG 600 system, the dissolution rates from those samples prepared at a higher temperature were faster than those prepared at the melting point of Gelucire. The dissolution rate increased with the amount of Gelucire added in the preparation. For the PVP/PEG 6000 carrier system, the dissolution rate of nifedipine increased with the amounts of both PVP and PEG 6000. However, a slower dissolution rate was also noted resulted from higher molecular weight of PVP.

Key words: solid dispersion, fusion, nifedipine, thermal analysis, dissolution

INTRODUCTION

The rate-determining step in the absorption process for poorly water-soluble drugs lies in their dissolution rate in gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall[(1)]. It is a major concern to improve the water solubility of insoluble and slightly soluble drugs. Crystalline drugs or excipients can be partially or completely transformed into metastable amorphous forms during processes such as milling, spraying, and lyophilization, commonly used in the manufacture of pharmaceutical solids[(2,3)]. The solubility, dissolution rate, and bioavailability of low-solubility drugs can be improved if the crystalline state is transformed into an amorphous one[(4)]. This is because a lower energy barrier needs to be overcome for a highly disordered amorphous material to enter solution than that for a structured crystalline solid has. To form a solid dispersion, one or more ingredients are dissolved or melted with inert carriers, including physiological surfactants[(4)], polymers[(5)], and other glass-formation solids. This is one of several techniques used to improve drug dissolution properties.

The goal of solid dispersions formation for any water-insoluble drug is to modify the crystalline form or to produce an amorphous form of the drug substances. The critical step in this process is to make the solid form of the drug substance dissolve or melt in the presence of hydrophilic carriers that shall prevent the formation of original crystalline structure, or transform it into a different crystalline form with a better solubility after solvent evaporation or after cooling. Traditionally, this is accomplished by dissolving the crystalline drug substance in a suitable solvent or mixture capable of dissolving the hydrophilic carriers (solvent method) or by heating both to melt (fusion method). Both methods have their own shortcomings. Solvents present health and environmental hazards. The high cost of disposal or recycling of large amount of solvents is a major concern if this method is employed to prepare solid dispersions. Minimizing or eliminating the usage of solvents will make this method more feasible. In the fusion method, a practical heating device should have a large enough capacity for scaled-up production and can also maintain a higher temperature. It would

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be beneficial to lower the fusion temperature for melting[6].

Nifedipine, a calcium channel blocker, is usually used in the treatment of a variety of cardiovascular diseases, such as angina pectoris and hypertension[7]. It is a photosensitive and poorly water-soluble drug with low bioavailability when orally administered in crystalline form[8]. To improve the dissolution rate, solid dispersions of nifedipine with water-soluble carriers such as urea[9,10], sucrose ester[11], solid polyethylene glycol (PEG)[9,10,12-14], polyvinylpyrrolidone (PVP)[10,14-16], polyvinyl acetate (PVA)[16], polyvinylpyrrolidone-co-vinylacetate (PVPVA)[14], Eudragit EPO[14], hydroxylpropylmethylcellulose (HPMC)[16,17], hydroxypropylmethylcellulose phthalate (HPMCP)[18], poloxamer[12,19,20], polyethylene oxide (PEO)[21], Gelucire[19], vitamin E TPGS[13], solutol HS-15[13], and insoluble carriers such as crospovidone[22] have been developed. Nevertheless, many solid dispersions were prepared by the solvent method[12,23-28], which raised both the environmental and health concerns discussed above.

In this study, solid dispersions of nifedipine with various water-soluble polymers as the combined carriers were prepared by a fusion method at low temperature or by a fusion/solvent method to minimize the quantities of solvents used. Based on the analysis by differential scanning calorimetry, phase diagrams were constructed to examine the influence of carriers on the change in fusion temperatures. Glass transition temperatures were obtained to understand the effects of carriers on the formation of the amorphous form of the model drug. Their dissolution profiles were examined with the aid of several additives to minimize the common tendency to aggregate, which occurred often during solid dispersions preparation with hydrophilic polymers.

MATERIALS AND METHODS

I. *Materials*

Nifedipine was obtained from Sunlite Chemical Industry (Japan). Gelucire 44/14 was supplied by Gattefosse (France). Gelucire® excipients are unique and consistent compositions of saturated polyglycolized glycerides, consisting of mono-, di- and tri-glycerides of saturated fatty acids, and of mono- and di-fatty acid esters of PEG. A Gelucire® is characterized by two values: its melting point and its hydrophilicity (by its HLB value), which determine its bio-pharmaceutical properties. These two figures are used to identify a Gelucire®: Gelucire® 44/14, for example, has a nominal melting point of 44°C and an HLB value of 14. PVP, K12-K30, was provided by ISP (Wayne, New Jersey, USA). HPMC, 6.5 cps, was obtained from Shin-Etsu (Tokyo, Japan). PEG 600 and PEG 6000 were of reagent grade and supplied by Merck (Darmstadt, Germany). Tween 80 was from Riedel-de Haën (Germany). Ethanol was from the Bureau of Wine and Tobacco Monopoly (Taiwan). All other materials were of reagent grade or better.

II. *Analysis of Differential Scanning Calorimetry (DSC) and Phase Diagrams*

DSC analyses were carried out on a DSC Pyris 1 (Perkin Elmer, USA). Approximately 10 mg of samples were heated at a rate of 10°C/min to 200°C (1st run). The fused samples were subsequently rapidly cooled to 10°C at a rate of 40°C/min, and then reheated to 200°C at a rate of 10°C/min (2nd run). The melting point was read at the peak of the line. Indium was used as the calibration standard.

Thermal analysis of a number of mixtures of nifedipine-Gelucire 44/14, nifedipine-PEG 600, or nifedipine-(Gelucire 44/14 : EG 600 = 4 : 1) of various compositions was conducted on the same DSC instrument (Pyris-1, Perkin Elmer). A phase diagram is composed of two lines. The line at the lower temperature is called the solidus line, which is obtained when mixtures begin to melt. The other line, called the liquidus line, is obtained when all mixtures have melted.

III. *Preparation of Solid Dispersions*

Solid dispersions of the PVP/PEG 6000 system were prepared by a fusion-solvent method. PEG 6000 and nifedipine were mixed and heated to a temperature high enough to melt both (110 - 170°C). A PVP/ethanol solution (50% w/w) was then added, and the dispersion was continually heated and stirred until most of the ethanol evaporated. The samples obtained by cooling to room temperature were exposed in a hot air oven to completely vaporize the residual ethanol. After vaporization, samples were milled to an extent that most particles could pass through a 100-mesh sieve. Solid dispersions of the Gelucire 44/14 and PEG 600 system prepared by the fusion method were produced in two ways. The first one was to heat the carrier to above their melting point (about 60°C) and then evenly distribute nifedipine into the carrier for 15 min. The other one was to mix the carrier with nifedipine first and then melt them together at a temperature higher than that at which both drug and carrier would melt. A fixed ratio (3 : 1) of these carrier systems (Gelucire 14/44, PEG 600, Gelucire 14/44/PEG 600 (4 : 1), and PVP/PEG 6000 (1 : 3)) to nifedipine was prepared.

IV. *Dissolution Studies*

The dissolution profiles of nifedipine from samples (an amount equivalent to 20 mg of nifedipine) were built at a temperature of 37 ± 0.5°C and a stirring rate of 50 or 100 rpm by the paddle method (USP XXIII) in 900 mL of HCl solution (pH 1.2) containing 1% w/v Tween 80. Samples were automatically withdrawn at predetermined intervals (5, 10, 15, 20, 40, and 60 min) and analyzed under the following HPLC conditions: a reverse -phase C18 column eluted by mobile phase (methanol : water : acetic acid : triethylamine = 65 : 35 : 1 : 0.03) at 1 mL/min and monitored at 280 nm[29]. The concentration of nifedipine was calculated based on a calibration curve constructed during each run. An average of at least three replicates was reported for each time point.

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The dissolution profile expressed as the cumulative release (%) versus time was plotted for comparison. The exposure to light was minimized during the process.

RESULTS AND DISCUSSION

In an attempt to lower the fusion temperature for preparing solid dispersions of nifedipine, thermal analysis of nifedipine in the presence of several polymers in an incremental series of weight fractions was conducted. Figure 1 shows the DSC thermograms of pure nifedipine for the 1st and 2nd heating runs. Thermograms of the 1st run indicated that the melting point of pure nifedipine is approximately 173°C as an endothermic peak. However, an exothermic peak around 109°C appeared in the 2nd run in addition to the endothermic melting peak of nifedipine. The 2nd run of the thermal analysis was executed after nifedipine had been melted at 200°C and then rapidly cooled to 25°C so that formation of amorphous form of nifedipine was expected. The phase transition peak at 109°C was, therefore, attributed to the transformation of the amorphous form of nifedipine to the crystalline form.

Figure 2A (1st run) and 2B (2nd run) illustrated the thermograms of nifedipine in the presence of PEG 6000 at percent weight fractions from 0 to 80%. Endothermic peaks at around 62 and 173°C in the 1st run thermograms represent the melting peaks of PEG 6000 and nifedipine, respectively. Only a sharp peak at the melting point of PEG 6000 was observed in the 1st run for samples containing 0 - 40% nifedipine. However, the melting peak of nifedipine gradually appeared in the 1st run thermograms when the percent weight fraction of nifedipine went up to 60 - 80%. In the thermograms of the 2nd run, the melting peak of PEG 6000 became broader and the peak height shifted to a lower temperature with an increase in the percent weight fraction of nifedipine from 0 to 40%. Similarly, the melting peak of nifedipine did not appear in thermograms of the 2nd run until the percent weight fraction was larger than 60%. The broadness of the melting peak of nifedipine in the 2nd run thermograms became more profound with increase in the percent weight fraction of PEG 6000. Exothermic peaks, as those in the 2nd run thermogram of pure nifedipine, also appeared in the 2nd run thermograms when the percent weight fraction of nifedipine exceeded 60%.

Theoretically, the broadness of the melting peak is related to the amount of dissolved impurities, as indicated in the van't Hoff equation[30], which describes the melting of a relatively pure material and the effect of impurities on the shape of a DSC scan. The melting peak of nifedipine disappeared in thermograms of both runs. They disappeared in samples with percent weight fractions of nifedipine from

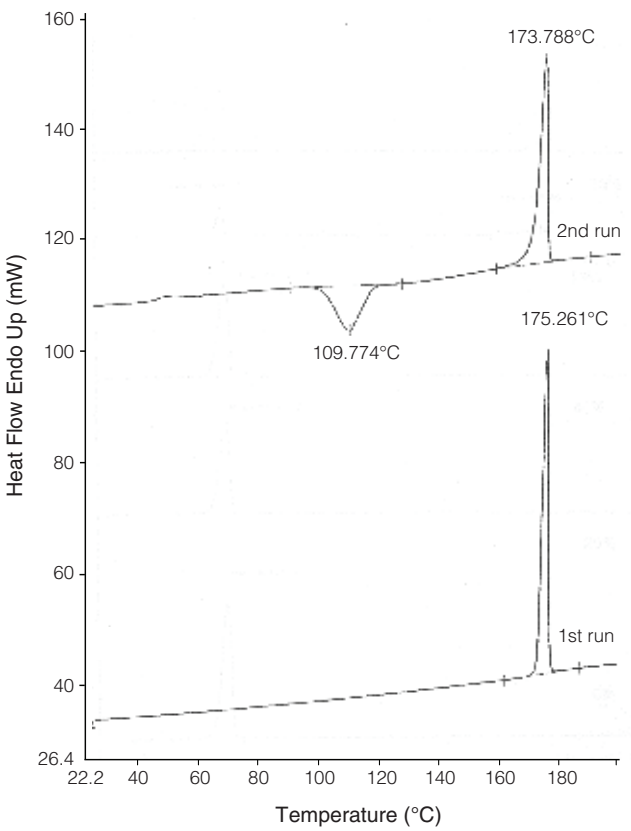

Figure 1. DSC thermograms of nifedipine.

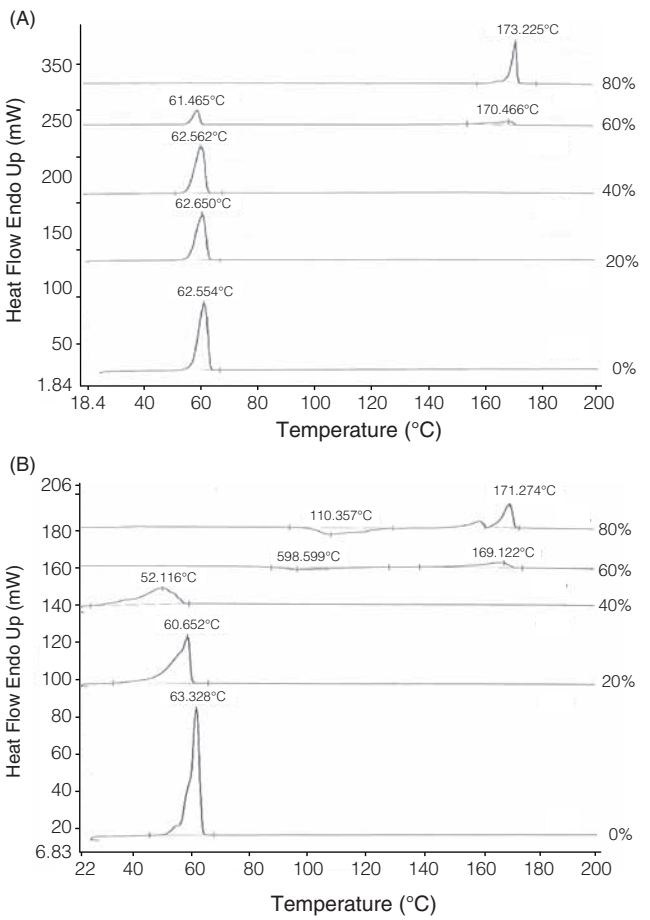

Figure 2. DSC thermograms of nifedipine and PEG 6000 mixtures heated for the 1st (A) and 2nd run (B).

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0 - 40% and the extent of broadness of the PEG 6000 melting peak in the 2nd run thermograms increased with the percent weight fraction of nifedipine. This indicated that nifedipine was dissolved in the melted PEG 6000 during the 1st run of heating, and the dissolved nifedipine appeared to interfere with the melting of PEG 6000 during the 2nd heating run. However, when the percent weight fraction of nifedipine exceeded 60%, the melted PEG 6000 was not soluble enough to completely dissolve nifedipine, resulting in the appearance of the nifedipine melting peak in thermograms of the 1st run and the exothermic peak indicating the transformation of the amorphous to the crystalline form of nifedipine in the 2nd run thermograms. This suggests that nifedipine is able to dissolve in fused PEG 6000 up to 60% weight fraction with no need of heating temperature close to the melting point of nifedipine.

Heating to approximately 110°C was tested to determine if it is sufficient to dissolve a 1 : 3 ratio of nifedipine to PEG 6000 completely. For manufacturing, a solid dispersion is preferred while prepared at a lower fusion temperature. Nifedipine can be dissolved in melted PEG 6000 at a weight percent of up to 60% so that it is not necessary to heat the sample up to the melting point of nifedipine. This would make preparation of solid dispersions by the fusion method more practical.

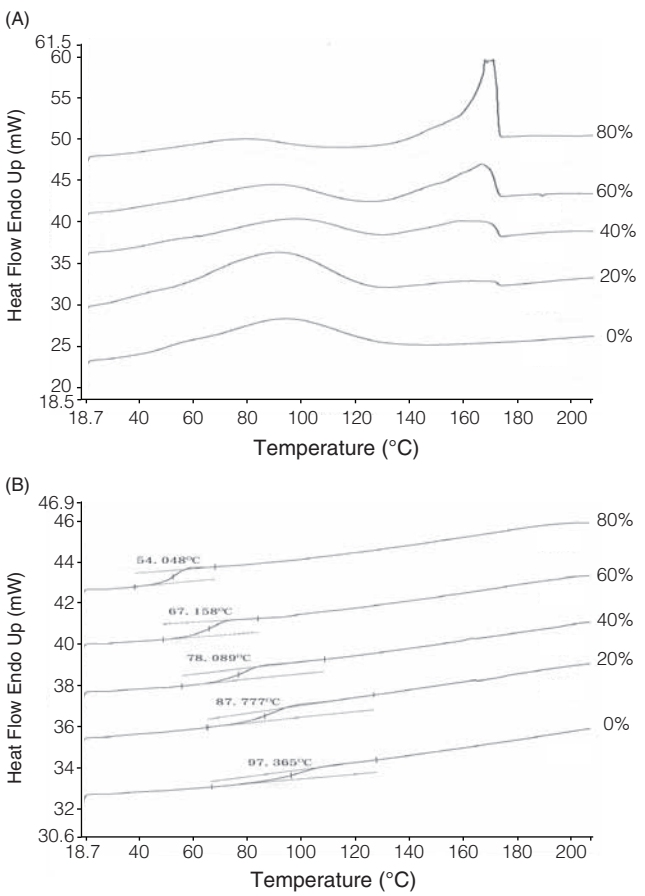

Figure 3. DSC thermograms of nifedipine and PVP K-12 mixtures heated for the 1st (A) and 2nd run (B).

Figure 3A (1st run) and 3B (2nd run) demonstrated thermograms of nifedipine in the presence of PVP (K-12) with incremental percent weight fractions of nifedipine. The 1st run thermograms showed a broad peak with a maximum near 90°C as the fusion peak of PVP. A broad to sharp peak at a temperature close to 170°C was the fusion peak of nifedipine. During the 2nd run, the glass transition temperature for PVP film reflected the film formation of the melted PVP after cooling. This transition temperature dropped as the percent weight fraction of nifedipine in the mixture increased. In contrast, the melting peak of nifedipine disappeared from the 2nd run thermograms for all nifedipine/PVP samples. The same phenomena were also observed when PVP K-12 was replaced with PVP K-17, K-25 or K-30.

Solublization of nifedipine in the melted PVP did not occur as fast as in melted PEG 6000, which caused a broad to sharp peak of nifedipine in thermograms of samples containing any percent weight fraction of nifedipine. However, the formation of crystalline nifedipine from melted nifedipine is completely prohibited by PVP after cooling for any percent weight fraction of nifedipine, which was evidenced as no exothermic peak for the transformation of amorphous to crystalline forms of nifedipine, and no corresponding melting peak of nifedipine in the 2nd run thermograms. Thus, PVP must reach its melting temperature to fuse nifedipine. Moreover, the crystallization of nifedipine from its melted form during cooling can be completely abolished by the fused PVP with the formation of a composite film.

The glass transition temperature of a polymer film is an indicator of its tensile strength. The higher the glass transition temperature, the higher the tensile strength of a polymer film. Figure 4 showed that the glass transition temperature of PVP film increased with higher molecular weight of PVP (K12 < K17 < K25 < K30), whereas increasing the fused amount of nifedipine in the PVP films lowered the glass transition temperature. In general, the higher the molecular weight of a polymer, the higher the tensile strength. This is consistent with the findings in Figure 4. In contrast, the

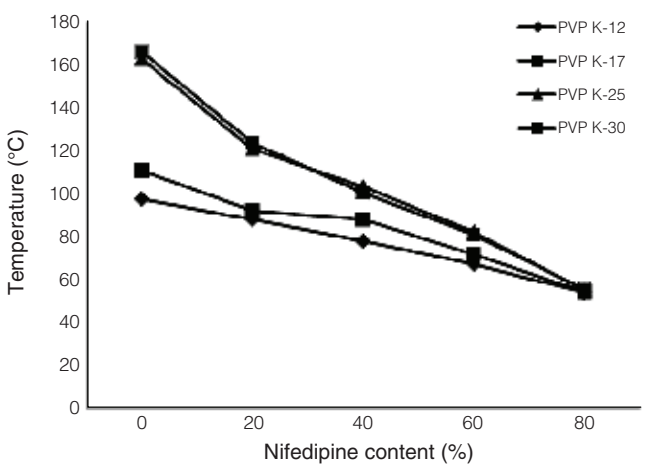

Figure 4. Glass transition temperature of PVP films with different K values in the presence of various amounts of nifedipine.

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presence of fused nifedipine in the PVP films played the role of impurity and weakened the structure of the polymer film, which resulted in a decrease in the glass transition temperature and an increase in the fused amount of nifedipine in the PVP films as predicted by the van't Hoff equation.

The phase diagrams of nifedipine with Gelucire 44/14, PEG 600, and Gelucire 44/14-PEG 6000 (4 : 1) were constructed. The diagrams showed that fusion temperatures of 151.4, 157.5, and 158.8°C for nifedipine in the presence of these hydrophilic carriers at nifedipine percent weight fractions of 40, 60, and 50%, respectively. Although these fusion temperatures are all lower than the melting point of nifedipine, the amount of decrease in the fusion temperature is no greater than that with PEG 6000, which could depress the fusion temperature of nifedipine to approximately 110°C.

Solid dispersions of nifedipine with PEG 6000 or PVP at a ratio of 1 : 3 were prepared by the fusion method as described above. However, the dissolution of solid dispersions of the former were not profoundly enhanced, even though nifedipine could be completely dissolved in melted PEG 6000 at a fusion temperature around 110°C, and the amorphous form of nifedipine could be maintained after cooling. In addition, the viscous nature of melted PVP, which was heated to the melting temperature of nifedipine, made the production of solid dispersions of nifedipine with PVP difficult and impractical, even though the dissolution of nifedipine was surely enhanced by PVP. A fusion-solvent method was proposed as described in the Material and Methods Section to prepare solid dispersions of nifedipine with PEG 6000 and PVP at a ratio of 1 : 3 : 1. PEG 6000 was used to lower the fusion temperature to a practical range. PVP was dissolved in ethanol to reduce the viscosity of the PVP and to uniformly mix it with the melted PEG 6000 while using less solvent.

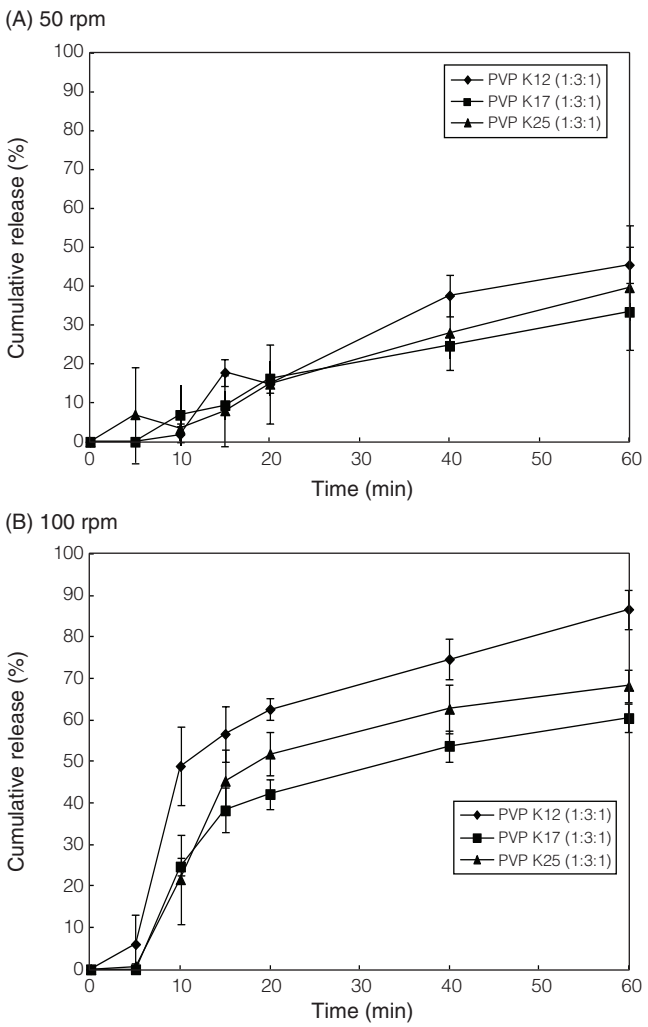

Figure 5. Dissolution profiles of nifedipine from solid dispersions prepared with PEG 6000 and various K values of PVP at a ratio of 3 : 1 with stirring at 50 (A) or 100 rpm (B).

The dissolution of nifedipine from solid dispersions prepared with several grades of PVP of different molecular weights (K12-K25) was compared with PEG 6000, by the fusion/solvent method, and Gelucire 44/14 and PEG 600, by the fusion method, at two different fusion temperatures. For the PEG 6000 and PVP system, Figure 5 showed that the smaller the K value of PVP, the faster the dissolution rate. Increasing the stirring rate of dissolution also increased the dissolution rate of nifedipine in all samples examined. PVP is characterized by its viscosity in aqueous solution, expressed as the K value, which is related to the molecular weight of PVP. Due to their viscous natures, PEG 6000 and PVP could enhance the adhesion among particles, which would make them difficult to disperse in the dissolution medium. Dissolution would, thus, be reduced due to the minimized surface area of particles. Expectedly, a lower K value of PVP with a lower viscosity and lower molecular weight would improve the dissolution of nifedipine from such a solid dispersion prepared with it. Without exception, this effect was also enhanced by a faster stirring rate.

Characteristics of the dissolution of nifedipine from the Gelucire 44/14 and PEG 600 system were given in Figure 6. The dissolution of mixtures prepared at higher temperature was faster than those prepared at the melting point of Gelucire 44/14. This enhancing effect on the dissolution rate was greater for Gelucire 44/14 than for PEG 600. The dissolution of nifedipine from a mixture of Gelucire 44/14 and PEG 600 (4 : 1) was slower than that from the Gelucire 44/14 system but faster than that from the PEG 600 system. In addition to the formation of a readily soluble nifedipine during the production of solid dispersions, the greater enhancement of the dissolution rate of nifedipine by Gelucire 44/14 and PEG 600 was also observed, possibly due to its wetting or solubilizing effect as a hydrophilic surfactant (HLB = 14) or solvent. As indicated by the phase diagrams, a fusion temperature higher than 150°C would be necessary to melt nifedipine crystals and transform them into an amorphous form, which would enhance the dissolution rate. Without the influence of fusion, nifedipine should dissolve at a similar rate from solid dispersions prepared at two different fusion temperatures. Nifedipine needs to be melted to enhance the dissolution rate because of it being transformed into a crystalline form with higher solubility. This explains why

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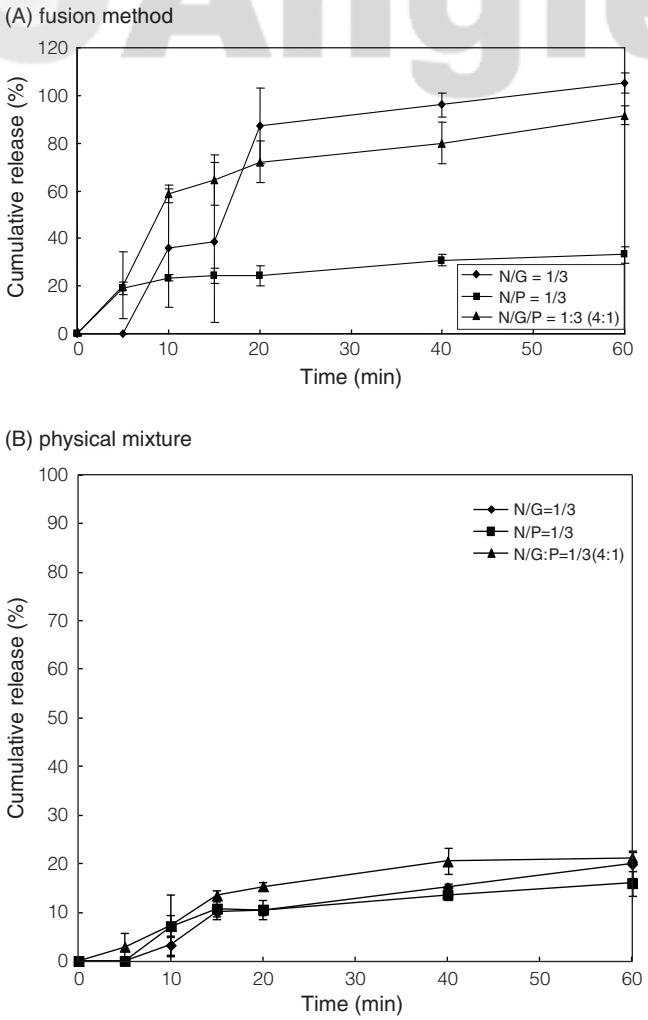

Figure 6. Dissolution profiles of nifedipine from solid dispersions prepared with Gelucire 44/14, PEG 6000, or Gelucire 44/14/PEG 6000 (4 : 1) fused at either the melting point of nifedipine (A) or Gelucire 44/14 (B).

the enhancement of the dissolution rate of nifedipine from solid dispersions containing Gelucire 44/14 and PEG 600 is not solely due to their wetting or solubilizing effects. The conclusion is that, dispersions must reach the fusion temperature in order to enhance the dissolution rate of a poorly soluble drug.

CONCLUSIONS

It was concluded that nifedipine could transform into a crystalline form of higher solubility at lower fusion temperature. This was found in the presence of PEG 6000, which made the preparation of solid dispersions of nifedipine by the fusion method more practical. This also demonstrated that it is critical to heat a poorly soluble drug to its fusion temperature so that it can cool in a crystalline form during the production of solid dispersions utilizing Gelcuire 44/14 and PEG 600 systems as carriers. PVP can prohibit the transformation of the amorphous form of nifedipine. PVP, however, is difficult to handle because of its viscosity and uneven distribution. A fusion/solvent method is thus proposed to eliminate this difficulty.

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