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Research paper

Preparation of a solid dispersion of felodipine using a solvent wetting method

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Abstract

A straightforward solvent wetting method was used to prepare felodipine solid dispersions in the presence of various carriers. Dichloromethane is not needed when HPMC solid dispersions were produced using the solvent wetting method. The amount of ethanol used to prepare solid dispersions did not have a significant effect on the dissolution rate of felodipine. The results of X-ray diffraction and thermal analysis indicated that the drug was in the amorphous state when PVP, HPMC, and poloxamer were used as carriers. The dissolution rates of felodipine in PVP, HPMC, or poloxamer solid dispersions were much faster than those for the corresponding physical mixtures. However, dissolution profiles were found to depend on the carrier used; the dissolution rate of felodipine increased slowly for solid dispersions prepared using HPMC, whereas rapid initial dissolution rates were observed for solid dispersions prepared using PVP or poloxamer. Increases in dissolution rates were partly dependent on the ratios of felodipine to carrier. No significant changes in crystal form were observed by X-ray diffraction or thermal analysis, and no significant changes in dissolution rate were observed when sorbitol and mannitol were used as carriers.

Keywords: Felodipine; Solid dispersion; Solvent wetting method; Dissolution; Poorly water-soluble

1. Introduction

Felodipine, a 1,4-dihydropyridine-derivative calcium-channel blocking agent, is widely used for the treatment of hypertension [1]. An enhancement of the dissolution rates of water-insoluble drugs remains one of the most challenging tasks of drug development, because the enhanced dissolution rates can increase drug oral bioavailability. Although felodipine is rapidly absorbed after oral administration, it is critical to improve the dissolution rate of felodipine to enhance the bioavailability due to its low solubility [2].

The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman [3] provides an efficient method to improve the dissolution rate of a drug [4,5]. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material. The mechanisms for the enhancement of the dissolution rate of solid dispersions have been proposed by several investigators. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates [6]. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process [7], and drug solubility and wettability may be increased by surrounding hydrophilic carriers [6].

The methods used to prepare solid dispersions include the melting method, the solvent method and the solvent wetting method [5,8]. However, the melting method and

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the solvent method have some limitations. In the case of the melting method, incomplete miscibility between drug and carrier may occur due to the high viscosity of a polymeric carrier in the molten state and thermally unstable drugs can be degraded due to the requirement of relatively high preparation temperatures. In the case of the solvent method, since both drug and carrier must be dissolved completely in organic solvent, subtle alterations in the conditions used for solvent evaporation may lead to large changes in product performance [5,9]. The solvent method also introduces residual solvent, which may bring up the environmental issues.

In this paper, a solvent wetting method was used to prepare solid dispersions of felodipine. This method requires the minimal amount of solvent in dissolving the drug. We used various polymeric carriers in this study. Polyvinylpyrrolidone (PVP), sorbitol, and mannitol were chosen as water-soluble polymers. Hydroxypropylmethylcellulose (HPMC) was chosen as a swelling and eroding polymer in water and poloxamer was chosen as an amphiphilic surfactant. The physicochemical properties of felodipine in solid dispersions were characterized by differential scanning calorimetry and powder X-ray diffraction, and the effects of various hydrophilic solid dispersion carriers on its dissolution properties were investigated.

2. Methods

2.1. Chemicals and reagents

Felodipine was obtained from Nanjing Machinery, Metals, Minerals, Medicines & Health products I./E. Corporation (Nanjing, China). Polyvinylpyrrolidone (Kollidon® K30) and poloxamer (Lutrol® F127) were provided by BASF (Ludwigshafen, Germany). Hydroxypropylmethylcellulose 2910 (HPMC) was provided by Shin-Etsu Chemical Co. (Tokyo, Japan). Mannitol and sorbitol were purchased from Junsei Chemical Co. (Tokyo, Japan). All other chemicals were of reagent grade and were used without further purification.

2.2. Preparation of physical mixtures

Physical mixtures were prepared by grinding felodipine and individual polymeric carriers in a mortar (the ratio of felodipine to polymer used was 1:5).

2.3. Preparation of solid dispersions by solvent wetting

Felodipine was dissolved in an appropriate amount of ethanol. The amount of ethanol used varied depending on the weight of drug and polymer. For PVP and HPMC, the amounts of ethanol used were 2.5 times the total weight of drug and polymer, and for the other cases, the amount of ethanol used was 1.5 times this. A mixture of ethanol and dichloromethane (1:1, v/v) or ethanol by itself was used to compare the solvent effects on the dissolution rate of drug, when HPMC was used as a carrier. After complete dissolution of felodipine, solutions were dropped onto polymeric carriers. Solvents were removed under vacuum at room temperature. The solid dispersions obtained were ground in a mortar.

2.4. Differential scanning calorimetry (DSC)

Thermal analyses were carried out using a DSC unit (DSC 50, Shimadzu Scientific Instruments, MD). Indium was used to calibrate the temperature scale and enthalpic response. Samples were placed in aluminum pans and heated at a scanning rate of 10 °C/min from 30 to 200 °C.

2.5. X-ray diffraction (XRD) patterns

X-ray powder diffraction was performed at room temperature with an X-ray diffractometer (X'Pert PRO MPD, PANalytical Co., Holland). Monochromatic Cu Kα-radiation ($\lambda = 1.5418$ Å) was obtained with a Ni-filtration and a system of diverging and receiving slides of 0.5° and 0.1 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 2θ range of 2–45° using a step size of 0.02° at a scan speed of 1 s/step.

2.6. Dissolution studies

Drug release tests were carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). The dissolution tester was calibrated using USP Dissolution Calibrator, salicylic acid (Lot O) and prednisone (Lot O0C056) tablets. Test samples containing 5 mg of felodipine were placed in a USP dissolution apparatus II containing 900 ml of distilled water at 37 °C (paddle method at 100 rpm). Samples were withdrawn at predetermined time intervals and equivalent amounts of distilled water were added. Samples were then centrifuged at 3000 rpm for 10 min, and the supernatants obtained were diluted with methanol. The centrifugation method was used instead of filtration due to the adsorption of felodipine to various filter papers. Felodipine in supernatants were analyzed by HPLC (Shimadzu Scientific Instruments, MD) at a wavelength of 238 nm and a flow rate of 1.2 ml/min (mobile phase; pH 3.5 phosphate buffer 0.1 M: methanol = 25:75). A calibration curve was constructed based on the peak height measurements. The limit of quantitation (LOQ) of felodipine was determined as the sample concentration resulting in peak heights of 10 times baseline noise. The LOQ was found to be 9 ng/ml. The intra- and inter-day precisions of the methods were determined by the assay of five samples of known concentrations of felodipine. The intra- and inter-day percentage of relative standard deviation (%) at concentration above LOQ was within 10%. The accuracy of felodipine ranged between 99.8% and 104.6%.

3. Results and discussion

The solid dispersions of felodipine were prepared by solvent wetting method which improves its dissolution rate and minimizes the problems associated with the solvent method. The solvent wetting method requires a minimal quantity of ethanol for the dissolution of felodipine, while both the drug and the carrier should be dissolved in a sufficient amount of solvent in case of solvent method. The effects of the amount of ethanol used to prepare solid dispersions on the dissolution rate of felodipine were investigated. No significant difference was observed in the dissolution rate on increasing the amount of ethanol from 1 to 2 μl/mg of polymeric carrier, indicating that the minimum amount of ethanol required to wet the polymeric carrier can be used to prepare solid dispersions of felodipine. The physical mixture of felodipine and various carriers, in which felodipine and each carrier was simply mixed, was also prepared to compare with solid dispersions.

The solid state characteristics of solid dispersions, were investigated using DSC and XRD to find out crystallinity of felodipine. The DSC thermograms of felodipine and of its solid dispersions are shown in Fig. 1. The sharp melting point peak of pure felodipine appeared at 145.6 °C, whereas no such peak was observed in solid dispersions prepared with PVP or HPMC, suggesting that felodipine was molecularly dispersed and in an amorphous form. However, in the case of the felodipine/sorbitol or felodipine/mannitol solid dispersions, a small felodipine melting point peak was observed, suggesting that some crystalline felodipine still remained. It was of interest to note that poloxamer melted at 55 °C and felodipine dissolved in the melted poloxamer solution. Consequently, the melting peak of felodipine did not appear.

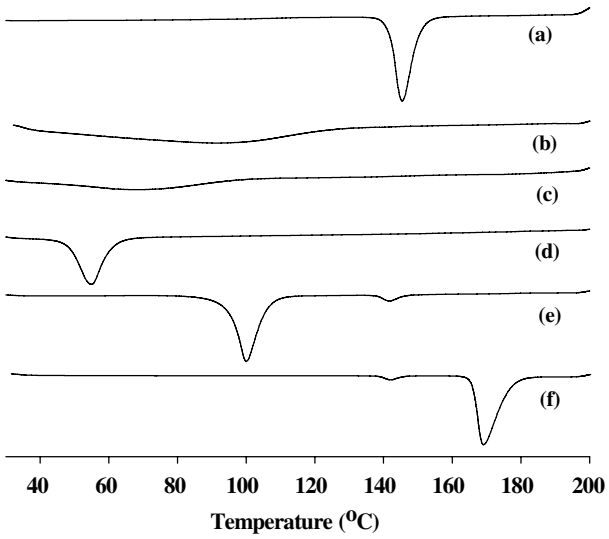

Fig. 1. DSC thermograms of felodipine and solid dispersions (SD) of felodipine. The ratio of felodipine to carrier was 1:5. (a) Felodipine (b) SD with PVP (c) SD with HPMC (d) SD with poloxamer (e) SD with sorbitol (f) SD with mannitol.

Since it was not possible to identify the crystallinity of felodipine in poloxamer by DSC, XRD was used to identify the crystallinity of felodipine, poloxamer, poloxamer/felodipine solid dispersion, and poloxamer/felodipine physical mixture; results are compared in Fig. 2A. Although the poloxamer solid dispersion showed traces of the characteristic peaks of felodipine, most of the crystallinity of felodipine disappeared. The XRD patterns of solid dispersions of felodipine with the other carriers are

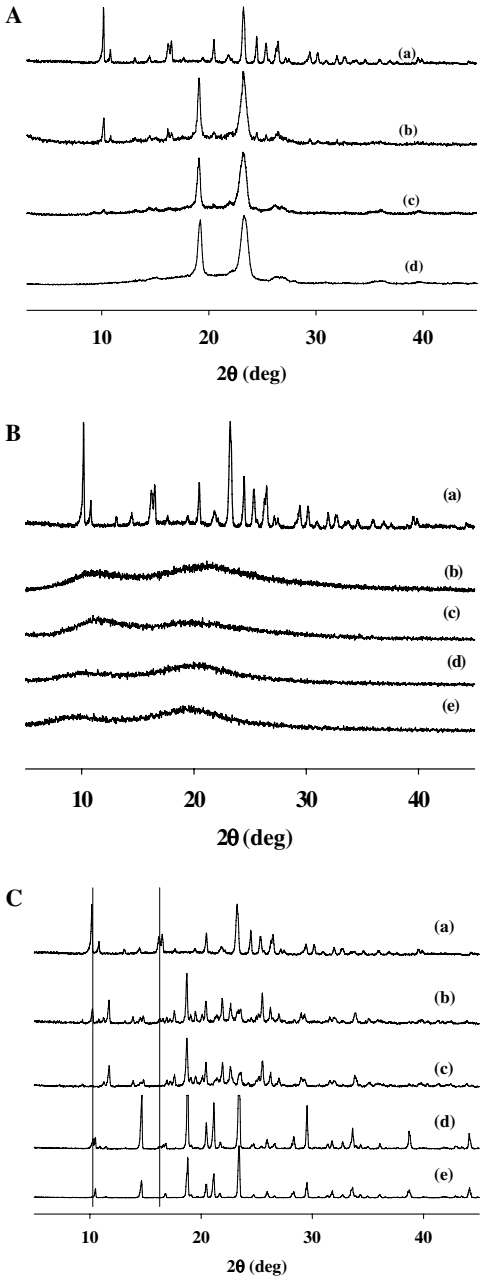

Fig. 2. X-ray diffraction patterns of felodipine, the individual carriers, and felodipine solid dispersions (SD) based on the individual carriers. The ratio of felodipine to carrier was 1:5 (wt/wt). (A) Felodipine (a), physical mixture of felodipine and poloxamer (b), SD with poloxamer (c), poloxamer (d); (B) felodipine (a), SD with PVP (b), PVP (c), SD with HPMC (d), HPMC (e); (C) felodipine (a) SD with sorbitol (b), sorbitol (c), SD with mannitol (d), mannitol (e).

shown in Fig. 2B. In the case of solid dispersions with PVP or HPMC, no characteristic felodipine peaks were observed. These results are in accord with previous DSC results, confirming that felodipine was transformed from a crystal to an amorphous form upon dispersion by the solvent wetting method. XRD patterns of solid dispersions of felodipine with sorbitol and mannitol are shown in the Fig. 2C. The unique felodipine peaks appeared at diffraction angles (2θ) of 10.8° and 17.6°. The analysis results of XRD indicated that the crystalline state was present in solid dispersions with sorbitol and mannitol, as was demonstrated by the DSC results.

Fig. 3 shows the dissolution profiles of felodipine from solid dispersions containing various ratios of felodipine to PVP and from a felodipine/PVP physical mixture (1–5). PVP is commonly used as a solid dispersion carrier to improve the dissolution rate of various water-insoluble drugs [5]. In the present study, the dissolution rates of felodipine from PVP solid dispersions were significantly faster than that of physical mixture. As the proportion of PVP increased, felodipine dissolution rates increased and reached a plateau at a ratio of 1:10. An increase in the dissolution rate of felodipine has been attributed to changes in its crystal form when prepared as a solid dispersion, which was confirmed by DSC and XRD results [5,10] and to enhanced wetting properties of PVP [10]. During the dissolution process of PVP solid dispersions, the concentration of felodipine in the medium reached 8 times the solubility of felodipine and then slightly decreased with time. In spite of this slight decrease, the concentration of felodipine was still much greater than its solubility at the end of dissolution study. It is clear that the recrystallization of felodipine was suppressed by PVP, which is known as an inhibitor of drug recrystallization [11,12].

HPMC has also been used as a solid dispersion carrier [13,14]. When HPMC is used as a carrier, a mixture of dichloromethane and ethanol has usually been added to dissolve the drug and the carrier [13,14]. However, dichloromethane is classified as a Class II solvent [15], whose usage should be avoided whenever possible [8]. Dichloromethane is required to dissolve HPMC since it has low solubility in ethanol. We examined whether ethanol by itself has the same effects as the mixture of dichloromethane and ethanol in the preparation of felodipine solid dispersion using the solvent wetting method. As can be seen in Fig. 4, no significant difference was observed in the dissolution rate of felodipine from solid dispersions prepared using ethanol or the mixture of dichloromethane and ethanol, indicating that dichloromethane could be avoided in the preparation of HPMC/felodipine solid dispersions using the solvent wetting method. It was also observed that the dissolution rates of felodipine from solid dispersions were markedly higher than for physical mixture. These increases in dissolution rates are attributable to changes in crystal structure, which were demonstrated by the results of DSC and XRD studies. Moreover, as the ratio of HPMC was increased, the dissolution rate of felodipine increased. Although both HPMC and PVP enhanced significantly the dissolution rate of felodipine, their dissolution profiles were quite different from each other, i.e., PVP solid dispersions showed rapid initial dissolution, whereas HPMC showed gradually increasing dissolution. HPMC is known to form a hydrogel [16,17] and to slowly erode in water, which probably explains this delayed dissolution.

Poloxamer is a water-soluble nonionic surface-active copolymer and has been used in solid dispersions to improve drug solubility [18–20]. Fig. 5 shows the dissolution rate of felodipine from solid dispersions prepared with poloxamer. The dissolution rates of felodipine from these solid dispersions were much higher than those from the physical mixture. The dissolution rate of felodipine from poloxamer solid dispersions was very rapid, and over 80% of the loaded drug dissolved in 1 h when the ratio of

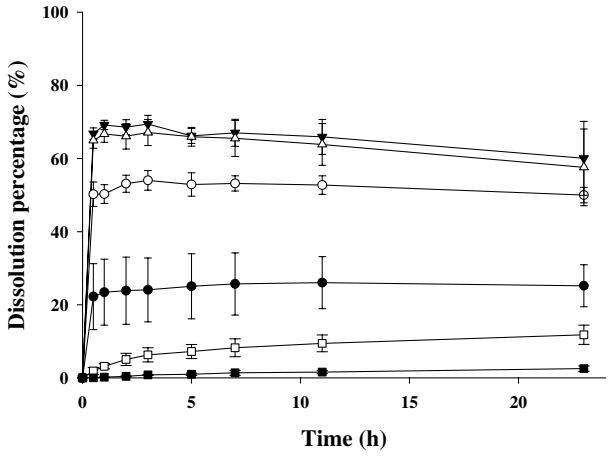

Fig. 3. Dissolution rate of felodipine from solid dispersions prepared using different ratios of felodipine to PVP. 1:3 (●); 1:5 (○); 1:10 (△); 1:15 (▼); a physical mixture; 1:5 (□) and crystalline felodipine (■). ($n = 3$).

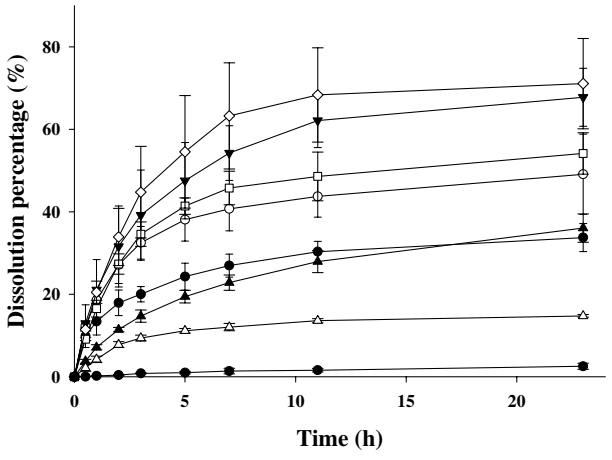

Fig. 4. Dissolution rate of felodipine from solid dispersions prepared using ethanol and dichloromethane with different ratios of felodipine to HPMC; 1:3 (●); 1:5 (□); 1:10 (◇), and prepared using ethanol with different ratios of felodipine to HPMC; 1:3 (▲); 1:5 (○); 1:10 (▼); physical mixture (△); crystalline felodipine (●). ($n = 3$).

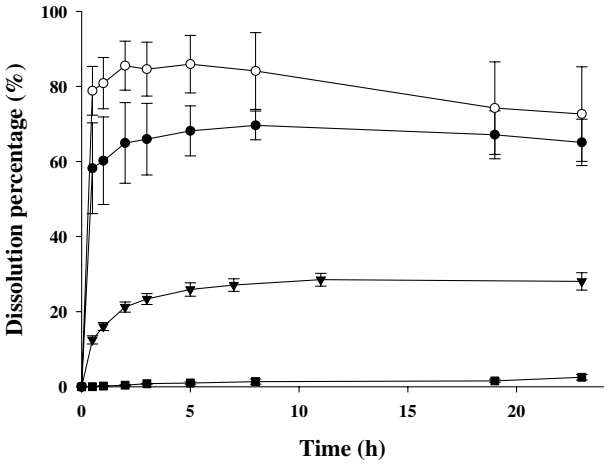

Fig. 5. Dissolution rate of felodipine from solid dispersions prepared using different ratios of felodipine to poloxamer; 1:3 (●); 1:5 (○); physical mixture; 1:5 (▼); crystalline felodipine (■). ($n = 3$).

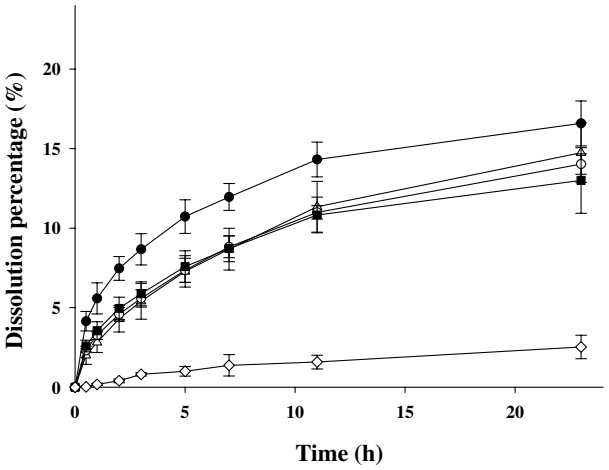

Fig. 7. Dissolution rate of felodipine from solid dispersions prepared using different ratios of felodipine to sorbitol; 1:5 (△); 1:10 (○), and felodipine to mannitol; 1:5 (▲); 1:10 (●); physical mixture with sorbitol; 1:5 (□); physical mixture with mannitol; 1:5 (■); crystalline felodipine (◇). ($n = 3$).

felodipine/poloxamer was 1:5. It was proposed that the amorphous state of felodipine in poloxamer solid dispersions and the solubilizing effect of poloxamer are attributable to the high dissolution rate [21]. Therefore, to further investigate the effect of poloxamer, we measured solubility of felodipine in the presence of 0.4 w/v % poloxamer and PVP at 37°C, since the solid dispersions prepared with poloxamer and PVP presented fast initial dissolution rate. The solubility of felodipine was greatly increased by poloxamer as shown in Fig. 6, whereas a little enhancement was observed with PVP. These results indicated that main mechanisms of increased dissolution rate of poloxamer solid dispersion were both solubility effect and the change in crystallinity, while that of PVP solid dispersion was the change in crystallinity.

Because sugars and their derivatives are highly water-soluble and have little toxicity, several attempts have been made to prepare a solid dispersion using them as a carrier [22,23]. The results of the study on the effects of sorbitol and mannitol as solid dispersion carriers on the dissolution rates of felodipine are shown in Fig. 7. Unlike the other carriers tested, both sorbitol and mannitol showed minimal increases in felodipine dissolution rate regardless of the drug/carrier ratio. The DSC and XRD studies show that the crystalline form of felodipine was present in these solid dispersions, which might explain the low dissolution rates of felodipine in sorbitol and mannitol solid dispersions. Although it is not clear why felodipine remained as a crystalline form in sorbitol and mannitol, it can be speculated that they are not compatible with each other and felodipine crystallizes shortly after felodipine was dispersed in sorbitol or mannitol. These results elucidate the importance of choosing an appropriate carrier and indicate that dissolution rates from solid dispersions are closely related with the unique property of individual carriers [22].

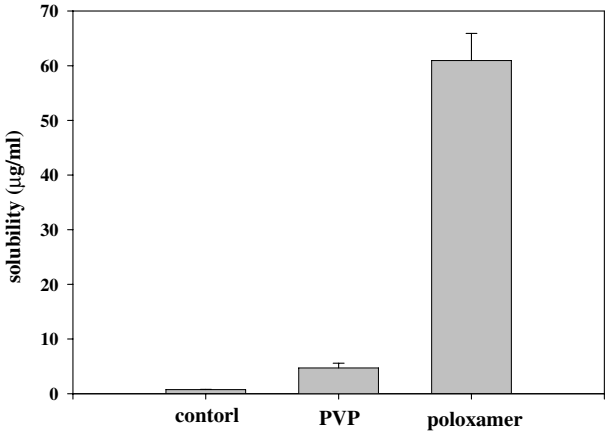

Fig. 6. The effect of 0.4 w/v % PVP and poloxamer on the solubility of felodipine at 37 °C. The control means the solubility of felodipine in water.

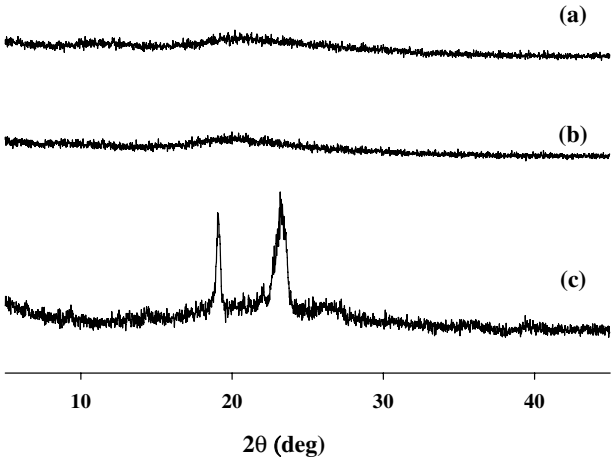

Fig. 8. X-ray diffraction patterns of felodipine after storage for over 3 months. The ratio of felodipine to carrier was 1:5 (wt/wt); solid dispersion (SD) with PVP (a), SD with HPMC (b), SD with poloxamer (c).

The short term physical stability of solid dispersions prepared in this study was investigated using XRD. The samples were stored at room temperature for over 3 months. As shown in Fig. 8, the solid dispersions of felodipine with HPMC, PVP, and poloxamer did not show any significant changes indicating recrystallization of felodipine. The long term physical stability is unknown at this point and will be investigated in the future.

4. Conclusion

Solid dispersions of felodipine were prepared using the solvent wetting method and various polymeric carriers. The results of DSC and XRD studies showed that felodipine in solid dispersions exists in the amorphous state in PVP, HPMC, and poloxamer, but not when sorbitol or mannitol is used as carriers. The dissolution rate of felodipine from PVP, HPMC, and poloxamer solid dispersions was markedly higher than from their corresponding physical mixtures. These results confirm that the solvent wetting method could be used to prepare felodipine solid dispersions using PVP, HPMC, and poloxamer as carriers, as a means of enhancing felodipine dissolution rates and of minimizing environmental issues.

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