

Preparation, characterization and tableting of cilnidipine solid dispersions

Liandong Hu^{1,2*}, Weihua Song^{1,2}, Feng Niu³, Kuiliang Jiao³ and Zheng Jia⁴

¹College of Pharmaceutical Sciences, Hebei University, Baoding, China

²Key Laboratory of Pharmaceutical Quality Control of Hebei Province, Hebei University, Baoding, China

³NBP Pharmaceutical Co. Ltd, CSPC Pharmaceutical Group Ltd, Shijiazhuang, China

⁴Department of clinical medicine, Tangshan vocational and technical College, Tangshan, China

Abstract: Solid dispersion technique has been developed many years for improving solubility of water-insoluble drugs, aiming to achieve a better oral bioavailability. However, this technique exhibits many inconveniences when used for large-scale tableting procedures. The objective of current research work was to develop cilnidipine solid dispersions (SDs) to improve the dissolution behaviors of this water-insoluble drug. Moreover, an innovative granulation method was designed to simplify the traditional tableting technology used in solid dispersion technique. Three different kinds of polymers, polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) and poloxamer, were used as carriers to prepare solid dispersions. The interactions in the solid state were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and FT-IR spectroscopy. The designed granulation method was employed to prepare solid dispersion tablets and the formulation was optimized through investigating the dissolution behaviors. The results indicated PEG solid dispersion showed the best effect both on physical characterizations and dissolution studies. Furthermore, all type of solid dispersions significantly improved the dissolution rates when compared to pure drug and its corresponding physical mixture (PM). The solid dispersion tablets prepared in simplified tableting method exhibited better operability, stability and dissolution behavior than the tablets prepared in traditional ways, which brought more opportunities to solid dispersion technique for industrial production.

Keywords: Cilnidipine; solid dispersion; dissolution; tableting; characterization.

INTRODUCTION

Cilnidipine, a novel dihydropyridine calcium channel blocker, has been reported to exhibit excellent clinical effects on cardiovascular diseases (Kitahara *et al.*, 2004; Minami *et al.*, 2000; Narita *et al.*, 2011). A unique pharmacological property for cilnidipine is that it inhibits both L-type and N-type calcium channels in various types of neurons (Konda *et al.*, 2006; Uneyama *et al.*, 1999). Recently, cilnidipine was found to possess much more unique advantages compared with traditional calcium-channel blockers (Takei *et al.*, 2009; Tanaka, 2010); for example, it causes a lower probability of reflex tachycardia and less effect on heart rate as compare to nifedipine (Minami *et al.*, 1998a; Minami *et al.*, 1998b). In addition, the renal protective effects of cilnidipine imply its great potency in benefiting hypertensive patients in altering their blood pressures (Kojima *et al.*, 2004; Konda *et al.*, 2006; Takei *et al.*, 2009; Tanaka, 2010). However, the dissolution and oral bioavailability of cilnidipine is not as good as expected, mainly because of its poorly water-soluble property.

Numerous methods have been developed to improve the dissolution of poorly water-soluble drugs (Barmapalexis *et al.*, 2011; Overhoff *et al.*, 2007; Shekunov *et al.*, 2006). The solid dispersion technique developed by Chiou and

Reigelman is one such method, which can provide an efficient method to enhance the dissolution rates and improve the oral bioavailability of a drug (Chiou and Reigelman, 1971; Shibata *et al.*, 2009; Vasconcelos *et al.*, 2007). In solid dispersion formulations, an amorphous or crystalline drug can be dispersed into an amorphous or semicrystalline polymer carrier (Kim *et al.*, 2006). Some compounds such as polyethylene glycol (PEG), poloxamer, polyvinylpyrrolidone (PVP), hydroxyl propyl methyl cellulose (HPMC) and even locust bean gum have been reported to be used as carriers (Kim *et al.*, 2006; Patel *et al.*, 2008; Shah *et al.*, 2009; Waghmare *et al.*, 2008).

In our research, the cilnidipine solid dispersions were prepared using different carriers (PEG, PVP and poloxamer) and the interactions in the solid state were characterized by DSC, PXRD and FT-IR. The differences between their physical mixtures and solid dispersions were investigated in order to choose the optimal carrier. The PEG and poloxamer solid dispersions were prepared via melting method and a solvent wetting method was used to prepare PVP solid dispersion. All the processes cilnidipine involved in were conducted in dark place, because of the light instability of cilnidipine. However, some problems such as poor compressibility and complex procedures, lead to handling difficulties in large-scale manufacturing involving solid dispersion tableting (Tran *et al.*, 2011). Therefore, an innovative attempt in our

*Corresponding author: e-mail: hbupharm@126.com

research was employed to simplify the tableting processes aiming to overcome the above difficulties. In addition, some comparisons were made to investigate the differences among the tablets prepared in such method and traditional ways.

MATERIALS AND METHODS

Materials

Cilnidipine was obtained from Anhui Bengbu Tushan Pharmaceutical Factory (Anhui, China); povidone (PVP K30) were provided by Tianjin Guangfu Fine Chemical Research Institute (Tianjin, China); Polyethy-lene glycol (PEG 6000) were purchased from Tianjin Yongda Chemical Reagent Co., Ltd (Tianjin, China); Poloxamer 188 was obtained as gift sample from Shenyang Pharmacy University Pharmaceutical Factory (Liaoning, China); Pregelatinized starch and crospovidone (PVPP) were kindly provided by Harbin Pharma-ceutical Group Co.,Ltd; Dehydrated alcohol was donated by Tianjin Jinfeng Chemical Co., Ltd (Tianjin, China). All other chemicals were of analytical grade and used without further purification. Distilled water was used throughout the study.

Preparation of physical mixtures

Physical mixtures were obtained by mixing required amount of cilnidipine and pulverized polymeric carriers (PEG, PVP or poloxamer) in a mortar for 15 min. The samples were stored in room temperature before used following passing through an 80 mesh sieve. The mixing ratio was 1:7 for cilnidipine to each polymer.

Preparation of solid dispersions and tableting

In melting method, PEG or poloxamer was heated in a water bath at 70°C to achieve completely melting initially. Cilnidipine was then added to the melt and stirred for ten minutes to obtain a transparent and clear homogeneous solution. The resultant dispersions were cooled at -10°C for 24 h and then pulverized via a Taisite pulverizer (Taisite, China). The 60-100 mesh fractions were sieved for further investigation. PVP was dissolved in equal weight ethanol firstly when solvent evaporation method was adopted and then the required amount of cilnidipine was added in. The solution was evaporated under 40°C following the homogeneous solution obtained and then dried in room temperature for 24 h. The pulverizing process was the same as above and the ratio of cilnidipine to each polymer was 1:7.

The cilnidipine solid dispersion tablets were prepared using wet granulation technique and ten thousand tablets were prepared for each formulation. The melting solid dispersion was served as adhesive for granulation directly, without the procedures of freezing and crushing in traditional solid dispersion tableting technology. Ethanol solution (50%, v/v) was used as wetting agent and 900 ml

was used for each formulation. A single punch tablet press (STF, China) equipped with a camber-faced punch (9 mm diameter) was used for tableting following the addition of magnesium stearate (1%, w/w) and polyvinyl pyrrolidone (4%, w/w). Each tablet weighed 200 mg and contained 5 mg cilnidipine, the tablet hardness was determined by a PYC-A hardness tablet tester (Shengjiang, China) and was in range of 55-65 N.

Differential scanning calorimetry (DSC)

Thermal analysis was carried out using differential scanning calorimetry. DSC determinations were conducted on a Shimadzu DSC-60 thermal analyzer (Shimadzu Corporation, Japan). Indium was used to calibrate for the temperature scale and energy. Accurately weighted amounts of samples were placed in perforated aluminium pans and heated at a scanning rate of 10°C/min from 40-140°C, under a nitrogen purge gas flow rate of 25 mL/min.

Powder X-ray diffraction (PXRD)

PXRD patterns of the raw materials, their physical mixtures, and the prepared solid dispersions were performed at room temperature with a Y-2000 Automated X-ray diffractometer system (Drigic, China). Monochromatic Cu K α -radiation ($\lambda=1.5406$ Å) was obtained with a Nickel-filtration, and a system of diverging and receiving slides were 1° and 0.2 mm, respectively. The patterns were recorded on a quartz plate at a tube voltage of 30 kV and a current of 20 mA over a 2θ range of 5-45° using a step size of 0.06° at a scan speed of 1 s/step. The peak intensities and 2θ values of the solid dispersion patterns were compared to those of the physical mixtures in order to evaluate the physical form of cilnidipine in the samples.

Fourier-transform infrared spectroscopy (FT-IR)

FT-IR spectra in the region of 400-4000 cm⁻¹ for samples were obtained using a FT-IR spectrometer-8400S (Shimadzu, Japan). The samples were previously grounded and mixed thoroughly with KBr in the ratio of 1:100. Twenty scans over the selected wave number range at a resolution of 4.0 cm⁻¹ were averaged for each sample.

Flowability

The flowability of different materials was characterized by determining angle of repose and compressibility index. The method of measuring angle of repose was established by pouring the materials through a funnel (inside diameter: 9 mm) onto a flat surface and determining the angle between the inclined plane and the horizontal plane. Compressibility index was calculated by using the following equation:

Compressibility index (%)=[(tapped bulk density-loose bulk density)/tapped bulk density] ×100

The loose bulk density was calculated through pouring

powers or granules (5g) into a calibrated measuring cylinder (20 ml). Two hundred tapping was continued until no further volume reduction in the cylinder. The finally constant volume was used to calculate the tapped bulk density.

Dissolution studies

Dissolution studies were carried out using a ZRS-8G dissolution apparatus (Haiyida, China). Test samples were tested at the paddle rotation speed of 75 rpm in 900 ml 0.4% lauryl sodium sulfate solution at $37 \pm 0.5^\circ\text{C}$. The samples were withdrawn at specified times and filtered through a membrane filter (pore size $0.45 \mu\text{m}$). The filtrates were subjected to HPLC (Shimadzu, Japan) equipped with a pump (LC-20AT) and a UV-Vis detector (SPD-20A). Chromatographic analysis was performed on a C18 analytical column. The mobile phase used was acetonitrile: 0.025 mol/L ammonium dihydrogen phosphate solution: Cyclohexane = 60:39:1. The flow rate was 1.0 ml/min, and the drug concentration was determined at 240 nm.

RESULTS

The DSC thermograms of pure drug, carriers (PEG, PVP and poloxamer), physical mixtures and solid dispersions were shown in fig 1. The unique melting peak of cilnidipine emerged at 109.86°C , and none of the solid dispersions prepared with PEG, PVP or poloxamer displayed such peak; in addition, there were some differences relating to the peak shapes and positions of three types of solid dispersions, when compared with the peaks of both carriers and physical mixtures.

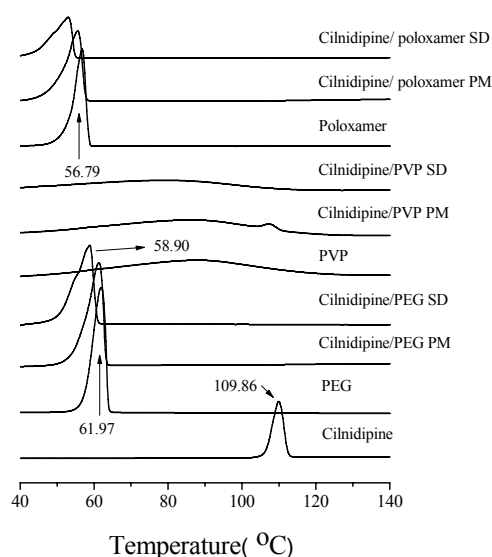


Fig. 1: DSC thermograms of pure drug, carriers, physical mixtures and solid dispersions

Fig. 2 showed the PXRD patterns of pure drug, carriers, physical mixtures and solid dispersions. The PXRD of cilnidipine exhibited characteristic sharp peaks at numerous 2θ values of 11.24, 13.64, 16.04, 18.44, 19.40, 21.32, 22.76, 23.72, 25.64, 26.60 and 29.00° , indicating its crystalline nature. Almost the entire characteristic peaks of cilnidipine were observed in the diffraction pattern of cilnidipine-PEG physical mixture, but the peaks became lower in fixed proportions. The PXRD patterns of the profiles relating to poloxamer were similar to the former group: the curve of cilnidipine-poloxamer physical mixture inherited all characteristic peaks of both cilnidipine and poloxamer, but the intensities of crystalline peaks were significantly less than that of intact cilnidipine. However, the patterns of PVP, cilnidipine-PVP physical mixture and cilnidipine-PVP solid dispersion were markedly different from the formers. Although most characteristic peaks of cilnidipine disappeared in the cilnidipine-PVP solid dispersion, some portions of such small peaks still existed in the curve.

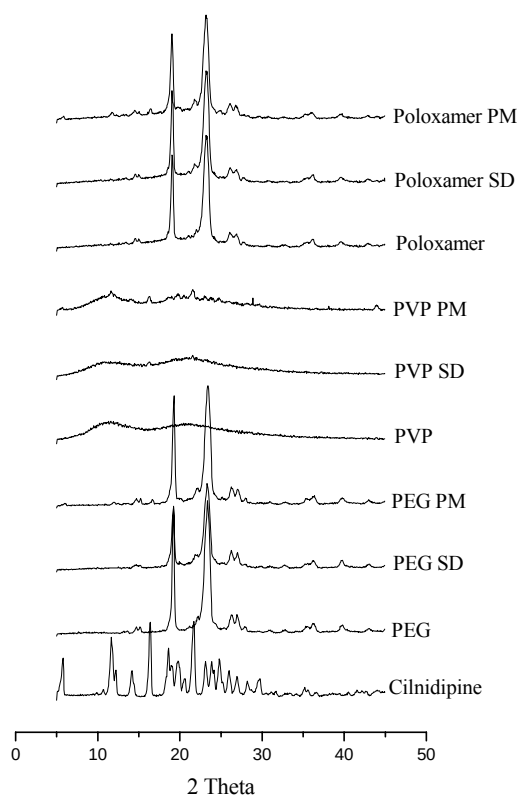


Fig. 2: PXRD of pure drug, carriers, physical mixtures and solid dispersions.

FT-IR spectra of the pure drug, carriers, physical mixtures and solid dispersions were illustrated in fig. 3. The most characteristic peaks of cilnidipine lay in the N-H stretch (3292 cm^{-1}) and the C=O stretch (1697 cm^{-1}), and the

molecular structure of cilnidipine was shown in fig. 4. The spectrum of physical mixtures was equivalent to the combination of the carriers and the crystalline drug. It was worth noting that the characteristic peaks at 3292 cm^{-1} and 1697 cm^{-1} were both disappeared in the curves of cilnidipine-PVP and cilnidipine-PEG solid dispersions. However, a distinct peak associated with C=O stretch of cilnidipine was emerged in cilnidipine-poloxamer solid dispersion.

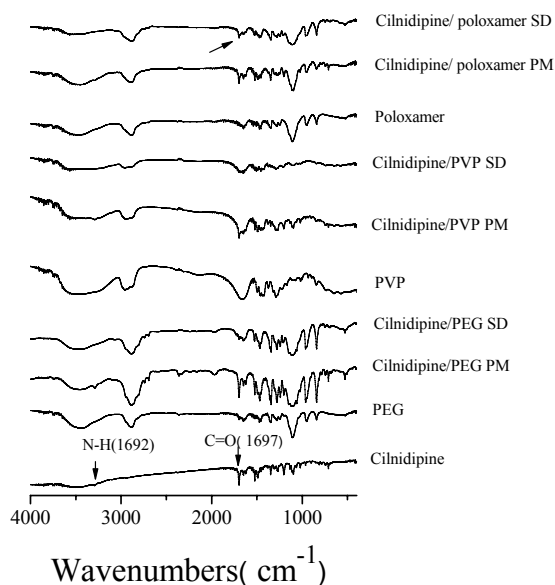


Fig. 3: FT-IR spectra of pure drug, carriers, physical mixtures and solid dispersions.

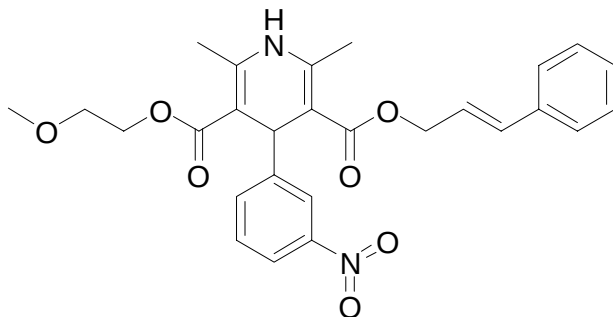


Fig. 4: Molecular structure of cilnidipine.

The power dissolution behaviors of pure drug, solid dispersions and physical mixtures were shown in fig 5. In all cases, each kind of solid dispersion exhibited markedly faster dissolution than that of pure drug and its corresponding physical mixture, indicating the remarkable effect of solid dispersion technique in promoting dissolution rates. In addition, over 90% of the loaded drug dissolved in less than 30 minutes for each kind of solid dispersion. The dissolution rates at 15 min for cilnidipine-

PVP solid dispersion was $88.10 \pm 4.02\%$, for cilnidipine-poloxamer solid dispersion was $89.80 \pm 4.21\%$, and for cilnidipine-PEG solid dispersion was $94.76 \pm 3.95\%$. The dissolution percent at 30min for cilnidipine-PVP solid dispersion was $91.26 \pm 4.27\%$, for cilnidipine-poloxamer solid dispersion was $95.74 \pm 3.73\%$, and for cilnidipine-PEG solid dispersion was $98.18 \pm 4.98\%$. The effect of the ratio of cilnidipine to PEG to dissolution rates was also evaluated, and the details were shown in fig. 6. The PEG solid dispersion powers were almost entirely dissolved in first 15 minutes and there were nearly no extra dissolutions in the next three points.

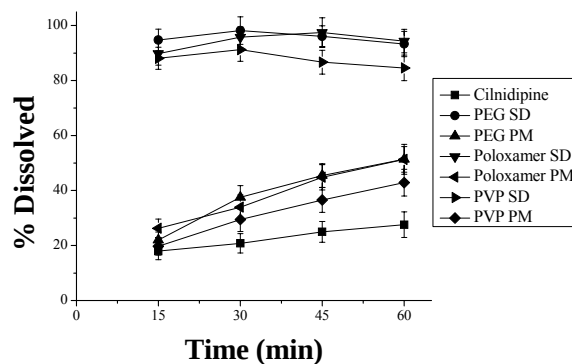


Fig. 5: Dissolution behaviors of pure drug, solid dispersions and physical mixtures.

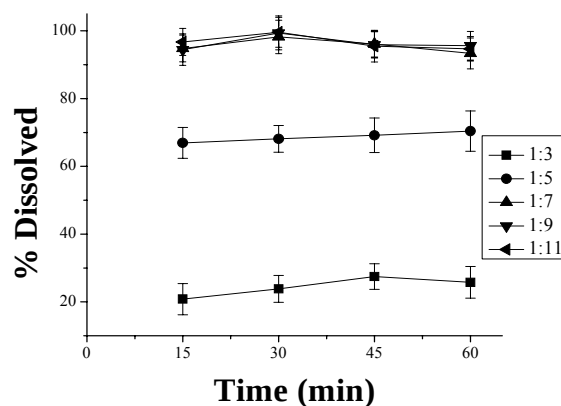


Fig. 6: Dissolution behaviors of the cilnidipine-PEG solid dispersions in different mixing ratios of cilnidipine to PEG

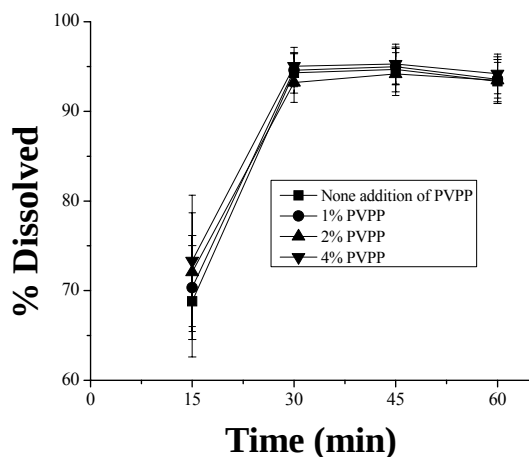
The statistics relating to powder properties were shown in table 1. The angle of repose for solid dispersion powers was found to be $21.0 \pm 1.46^\circ$, but the low compressibility index ($9.14 \pm 0.99\%$) suggested poor compactibility of the powers into tablets; therefore, some methods must be adopted to improve the flowability of solid dispersions, such as granulating or adding excipients.

Table 1: Flowability of related powders and granules

	Angle of repose(°)	Compressibility index (%)
Starch powders	35.1 ± 1.55	24.00 ± 1.82
Starch granules	28.0 ± 1.43	19.78 ± 0.82
PEG SD powders	21.0 ± 1.46	9.14 ± 0.99
PEG SD granules	29.1 ± 1.26	20.26 ± 0.93

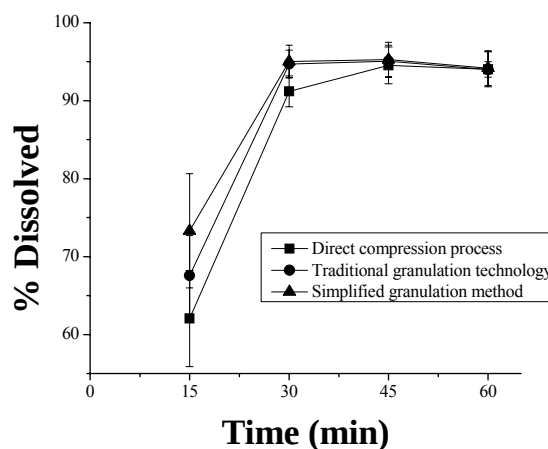
Lactose was given priority to serve as the excipient for tableting because of its good solubility in water, but the tablets prepared with lactose presented to be abnormal yellowish in color when stored at 25°C without light. Therefore, pregelatinized starch was employed to replace lactose as the excipient; in addition, the angle of repose ($35.1 \pm 1.55^\circ$) and compressibility index ($24.00 \pm 1.82\%$) values demonstrated its good fluidity and compressibility. The dried granules prepared in proposed technique exhibited similar angle of repose ($29.1 \pm 1.26^\circ$) and compressibility index ($20.26 \pm 0.94\%$) to pregelatinized starch granules ($28.0 \pm 1.43^\circ$, $19.78 \pm 0.82\%$).

PVPP was a commonly used disintegrant agent in tableting, due to its good swelling property and low stickiness. For this reason, the effect of PVPP concentration (0, 1, 2 and 4%) on the dissolution behaviors was evaluated, and the details were shown in fig. 7. As the percent of PVPP occupied was increased from 0 to 4%, the dissolution rate was also increased, and the effectiveness was mainly reflected in 15min. Drug dissolution at this point in the above formulations was $68.81 \pm 6.21\%$, $70.34 \pm 5.80\%$, $72.05 \pm 6.62\%$ and $73.31 \pm 7.33\%$, respectively.

**Fig. 7:** Dissolution behaviors of solid dispersion tablets with different amount of PVPP

The dissolution behaviors of three kinds of tablets prepared via three different methods, direct compression process (labeled as T1), traditional granulation technology

(labeled as T2), and simplified granulation method (labeled as T3), were shown in fig. 8. The tablet prepared in simplified granulation method exhibited a better dissolution behavior than the others, especially demonstrated by the dissolution rates at 15min. The dissolution rates at 15min were $62.06 \pm 6.17\%$ for T1, $67.55 \pm 5.14\%$ for T2, and $73.31 \pm 7.33\%$ for T3. In addition, the dissolution rates at 30min were $91.20 \pm 1.98\%$, $94.71 \pm 1.77\%$, and $95.04 \pm 2.09\%$.

**Fig. 8:** Dissolution behaviors of three kinds of tablets prepared via three different methods

DISCUSSION

In DSC spectra, it was of notable that the endothermic peak of cilnidipine disappeared from both the curves of the cilnidipine-PEG and the cilnidipine-poloxamer physical mixtures, similar as their solid dispersions; but such peak appeared in the curve of the cilnidipine-PVP physical mixture. Compared with cilnidipine, the two distinct peaks emerged at 61.97°C and 56.79°C indicated the much lower melting points of PEG and poloxamer. Therefore, the long time melting state of PEG and poloxamer stood a good chance of dissolving the drug, resulting in the disappearance of the cilnidipine endothermic peak. Unlike the curves of PEG and poloxamer, PVP exhibited an entirely different behavior in melting process. In the curve of PVP, the broad endothermic peak tending to a straight line suggested a much longer melting process and a higher melting point than PEG and poloxamer. Just for this reason, the PVP solid dispersion was prepared using solvent evaporation method, aiming to avoid the degradation caused by high temperature when melting method was used. Several researchers reported the presence of broad endothermic peak of PVP in DSC thermogram (Weuts *et al.*, 2005; Zhang *et al.*, 2008), and the reason was mainly due to the hygroscopicity of PVP. Therefore, it was lack of the opportunity to dissolve the drug, just because of the long

melting process and the higher melting point for PVP. Consequently, a small cilnidipine melting point peak was observed in the curve of cilnidipine-PVP physical mixture, suggesting the crystal form of cilnidipine was still partly existing. Based on the distinctions between physical mixtures and solid dispersions, the DSC results suggested that the cilnidipine was molecularly dispersed into the polymer matrixes in PVP solid dispersion, but it is hard to judge whether the solid dispersions are formed in other cases. Therefore, above samples were also evaluated through PXRD analysis in the following investigation to identifying the crystalline of cilnidipine, carrier, physical mixtures and solid dispersions.

The PXRD results indicated that the crystalline nature of the drug was still maintained, and did not change in the physical mixtures. However, the curves of cilnidipine-PEG and cilnidipine-poloxamer solid dispersions were in strong similarities with their polymers, and the characteristic sharp peaks of them were observed at the similar 2 θ values. It was worth noting that the entire characteristic peaks of cilnidipine disappeared in the curve of cilnidipine-PEG and cilnidipine-poloxamer solid dispersion, but such disappeared peaks were detected in each curve of physical mixtures. The above results indicated that the cilnidipine-PEG and cilnidipine-poloxamer physical mixtures were still simple superpositions of each component, but the original crystal structure of cilnidipine was not existed in the solid dispersions, and the new solid phase had been formed. However, the patterns of PVP, cilnidipine-PVP physical mixture and cilnidipine-PVP solid dispersion indicated that cilnidipine still partly existed in the crystalline form with reduced crystal size in the cilnidipine-PVP solid dispersion.

The FT-IR spectra indicated that the spectrum of physical mixtures was equivalent to the combination of the carriers and the crystalline drug. The disappearance of the N-H stretch (3292 cm⁻¹) and the C=O stretch (1697 cm⁻¹) suggested that there were some sort of solid-state interactions between cilnidipine and the carriers. The spectra of cilnidipine-poloxamer solid dispersion suggested a weaker interaction compared with cilnidipine-PVP and cilnidipine-PEG solid dispersions. In addition, no additional peak was detected in all FT-IR spectra, indicating absence of any chemical reactions between cilnidipine and carriers. Considering all above results (DSC thermograms, PXRD patterns and FT-IR spectra), cilnidipine-PEG solid dispersion was the unique formulation which exhibiting good solid-state interactions in all terms.

The dissolution pattern of cilnidipine was found to be very slow, in accordance with its poorly water-soluble property. The detailed statistics showed a more effective promotion of cilnidipine-PEG solid dispersion than the others. The rapid dissolution rates were attributed to the

good solubilizing effect of PEG and the solid dispersion technique. The increase amount of PEG contributed a significant promotion to dissolution rates from 1:3 to 1:7, but the trend turned to be subtle from 1:7 to 1:11 and there was no significant difference among the three. Therefore, we can conclude that PEG maximized its effectiveness in promoting dissolution rates in the ratio of 1:7, and this ratio was chosen for further investigation and tableting.

When the direct compression process was used for the mixing powers (pregelatinized starch and solid dispersion), the rise in temperature caused by the frequent friction and compression could resulted in an increase of stickiness of solid dispersion powers. This problem was mainly due to the low melting point (58.90°C) detected in DSC investigations fig. 1, and finally resulted in high weight variation and poor content uniformity if not solved.

Therefore, wet granulation technique was employed to continue our research. In traditional method used for solid dispersion granulation, pulverized solid dispersions were mixed with diluent agent firstly, and then adhesive was added to the above materials to achieve granules. Lubricant and disintegrant were added before tableting. Our research offered a novel method for solid dispersion granulation, and the time and complexity in progress were both reduced. The melting solid dispersion was poured into sieved pregelatinized starch directly for granulation as adhesive, without the procedures of freezing and pulverizing in traditional solid dispersion tableting technology, which was the most important procedure in the whole technology. The amount of pregelatinized starch should be enough to suit the stickiness of the melting solid dispersion, or an insufficiency may lead to high hardness of the granules. The stirring rate must be high enough to achieve blending completed; otherwise, the rapid clump and agglomerate may result in poor content uniformity. The drying temperature should be relative low in order to avoid a remelting of the solid dispersions. The dried granules prepared in proposed technique exhibited good flowability and compressibility. In addition, the problems, such as sticking, weight's imparity and weight variation emerged in the direct compression process, had been solved through wet granulation technique.

The investigation of PVPP suggested the addition of PVPP exhibited a promotive action to dissolution, and the dissolution behaviors turned to be better with the increase of proportion of PVPP. Therefore, 4% PVPP was employed for tableting to achieve the optimum effect. The dissolution behaviors of three kinds of tablets prepared via three different methods indicated the simplified granulation method exhibited both better operability and dissolution behaviors than the traditional ways.

CONCLUSION

The research demonstrated the PEG was the most appropriate carrier among the three (PEG, PVP and poloxamer) for preparing cilnidipine solid dispersions via the investigations of DSC, PXRD, FTIR and the dissolution behaviors; in addition, the ratio 1:7 of cilnidipine to PEG was the most appropriate use level. Each kind of solid dispersion exhibited markedly higher dissolution behavior than that of pure drug and its corresponding physical mixture, fully confirming the conspicuous actions in improving the dissolution of poorly water-soluble drugs. The final tableting formulation and the simplified process both had tremendous potentials in commercial large-scale production. Furthermore, it needs more research to verify whether the simplified tableting method used to solid dispersion technique could be applied to more kinds of drugs or polymers.

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