Application of Nilvadipine Solid Dispersion to Tablet Formulation and Manufacturing Using Crospovidone and Methylcellulose as Dispersion Carriers

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Nilvadipine (NIL) solid dispersion using crospovidone (Cross-linked-*N*-vinyl-2-pyrolidone, cl-PVP) and methylcellulose (MC) as carriers was applied to tablet formulation. Several grades of cl-PVP and MC were used, and their influence on tablet properties such as hardness, disintegration, dissolution and chemical stability were investigated. The agitation granulation method was used for preparation of solid dispersion granules, and the granules were compressed using a rotary tableting machine, and finally the obtained tablets were coated with film. As the particle size of cl-PVP decreased, hardness and apparent solubility were increased, while dissolution rate was lowered. When a higher viscosity grade of MC was used, hardness and dissolution rate were increased, and apparent solubility did not change. All batches of tablets were chemically stable at 40 °C, 75% relative humidity (R.H.) for six months. Finally, tablets with enhanced dissolution properties were obtained by using Polyplasdone XL-10 and Metolose SM-25 as the grades of cl-PVP and MC, respectively. These formulation tablets showed higher solubility and dissolution rate during storage as well as initial indicating good physical stability.

Key words nilvadipine; solid dispersion; tablet; dissolution

The solid dispersion technique has been widely used to improve the dissolution rate and bioavailability of poorly water-soluble drugs.[1,2] However, there are very few marketed products utilizing this technique, due to dissolution instability and manufacturing difficulties. Manufacturing difficulties may be related to the soft and tacky nature of solid dispersion, and there may be a lack of disintegration and slow dissolution of tablets prepared from solid dispersion.[3] However, drugs must be developed into convenient form such as tablets and capsules for clinical use and successful commercialization. Therefore, simple manufacturing and formulation of tablets with enhanced dissolution would be a great advance in solid dispersion technology.

In the previous study,[4] we obtained an ideal solid dispersion which had a consistently high rate of dissolution by the use of ternary solid dispersion systems comprising nilvadipine (NIL), crospovidone (cl-PVP) and methylcellulose (MC). In this study, we applied the stable ternary solid dispersion systems to the tablet dosage form. Several grades of cl-PVP and MC were used, and their influence on tablet properties such as hardness, disintegration, dissolution, chemical stability and dissolution stability were investigated.

Experimental

Materials Nilvadipine (NIL, Sagami Chemical Industry Co., Ltd., Japan), four grades of cl-PVP (Kollidon CL, BASF Japan Ltd., Japan), (Polyplasdone XL, XL-10 and INF-10, ISP Japan Ltd., Japan), two grades of MC (Metolose SM-15 (MC15) and SM-25 (MC25), with designated viscosity for a 2% (w/v) aqueous solution of 15 and 25 mm^2/s, respectively, Shin-Etsu Chemical Co., Ltd., Japan), lactose (Lac, Freund Industrial Co., Ltd., Japan), low-substituted hydroxypropyl cellulose (L-HPC, Shin-Etsu Chemical Co., Ltd., Japan), magnesium stearate (Mg-st, NOF Corp., Japan), hydroxypropylmethylcellulose (HPMC, Shin-Etsu Chemical Co., Ltd., Japan), polyethylene glycol (PEG, NOF Corp., Japan), titanium oxide (TiO_2, Ishihara Sangyo Kaisha Ltd., Japan), and talc (Hayashi Kasei, Japan) were used. Other chemicals used were of reagent grade.

Preparation of Solid Dispersion Granules NIL (10 g) was dissolved in ethanol (400 g), and then cl-PVP (40 g) and MC (40 g) were suspended in this solution to obtain granulating fluid. Half of this granulating fluid was added to the mixture of Lac (195 g), L-HPC (125 g) and MC (30 g), and then the mixture was granulated for 5 min with a high-speed agitation granulator (High-Speed Mixer, Fukae Pawtech Corp., Japan) at the rates of 600 rpm with an agitator and 2400 rpm with a chopper. The resulting granules were dried with a fluidized bed drying machine (MP-01, Powrex Corp., Japan) and sieved with a 22 mesh sieve (sieve opening 710 μm). The dried granules were reprocessed in a high-speed agitation granulator again, and the residual granulating fluid was added to the reprocessed granules, and then the mixture was granulated, dried and sieved by the above-mentioned procedures. The solid dispersion granules were thereby obtained.

Preparation of Tablets Before compression, the solid dispersion granules (440 g) were mixed with Mg-st (5 g) in a polyethylene bag for 1 min. The tablets were compressed using a rotary tableting machine (AQUARIUS-0518, Kikusui Seisakusho Ltd., Japan) using bi-convex punches 8 mm in diameter at rotating speed of 15 rpm. All batches of tablets weighed 178 mg and the target compression load for each batch was 700, 1300 or 1600 kg.

Preparation of Film-Coated Tablets Film coating was performed using a Hicoater (HCT-30, Freund Industrial Co., Ltd., Japan), and all batches of core tablets were compressed at 1300 kg. The amount of film coating was 10 mg per tablet and the coating solution consisted of the following ingredients: HPMC (9.5%), PEG (2.2%), TiO_2 (2.2%), talc (0.7%) and purified water (q.s. 100%).

Hardness Test of Tablets Hardness of the tablets was measured by the diametral compression method with a TM3-3 (Kikusui Seisakusho Ltd., Japan). Twenty tablets were tested in each batch, and means were calculated.

Disintegration Test of Tablets Disintegration time of the tablets was measured individually on six tablets in purified water at 37±0.5 °C using the JP 14 apparatus (NT-2HS, Toyama Sangyo Co., Ltd., Japan), and means were calculated.

Dissolution Test of Tablets Dissolution tests were performed using the JP14 apparatus (NTR-6100, Toyama Sangyo Co., Ltd., Japan). One tablet containing 4 mg of NIL was put into the dissolution medium (900 ml of purified water) at 37±0.5 °C, and the paddle was rotated at 50 rpm. The amount of dissolved NIL was determined with an ultraviolet spectrophotometer (UV-1600, Shimadzu Corp., Japan) at 242 nm. Three tablets were tested in each batch, and means were calculated.

Particle Size Analysis Particle size of cl-PVP was determined by the laser diffraction method using a laser diffraction particle size analyzer (SALD-2000A, Shimadzu Corp., Japan).

Storage Condition of Stability Test In order to study chemical and physical stability, the solid dispersion tablets were stored in an aluminum–polyethylene bag at 40 °C, 75% relative humidity (R.H).

Chemical Stability (Assay) Twenty tablets were crushed and a portion of the powder equivalent to 4 mg of NIL was carefully weighed, supple-

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mented with exactly 10 ml of the internal standard solution, and then with diluted acetonitrile (1 in 2) to make the volume 100 ml, sonicated, and centrifuged. The supernatant liquid was used as the sample solution, and the content of NIL was assayed by HPLC. The HPLC system consisted of a pump (L-7100, Hitachi Ltd., Japan), a detector (UV-8000, Tosoh Corp., Japan), an auto injector (AS-8020, Tosoh Corp., Japan) and an integrator (C-R6A, Shimadzu Corp., Japan). The mobile phase was prepared as follows: 1.25 g of diammonium hydrogen phosphate was dissolved in 500 ml of purified water and supplemented with 5 ml of tetra-*n*-butyl ammonium hydroxide test solution, and the pH of this solution was adjusted to 7.0 by adding diluted phosphoric acid (1 in 10); then 600 ml of acetonitrile was added to the solution. An acetonitrile solution of acenaphthene (1 in 313) was used for the internal standard solution. The detector was operated at a wave length of 254 nm. The flow rate was 1 ml/min through the column (YMC-Pack, ODS-A, 4.6 mm×150 mm, YMC Co., Ltd., Japan).

Physical Stability (Dissolution) Solid dispersion often shows poor dissolution stability during storage. Therefore, to investigate dissolution stability of NIL solid dispersion tablets during storage, we performed dissolution test. The apparatus and test conditions were same as "Dissolution test of tablets" mentioned above. At 30 min, aliquots of the sample solution were taken and filtered through a 0.45 μm-membrane filter (DISMIC-25HP, Toyo Roshi Kaisha, Ltd), and concentration of NIL was assayed by HPLC. A mixture of pH 7.4 phosphate buffer solution/methanol/acetonitrile (7 : 7 : 6) was used as the mobile phase. Flow rate was 1 ml/min and operated at 242 nm. The HPLC system was same as chemical stability.

Results and Discussion

Manufacturing of NIL Solid Dispersion Tablets We selected ethanol as a solvent in preparation with solid dispersion granules. From point of the solubility of NIL, dichloromethane has a higher solubility than ethanol. However, dichloromethane is known for a more toxic solvent than ethanol, therefore we selected ethanol as a solvent. To prepare the solid dispersion granules, the agitation granulation method was applied, and the manufacturing process consisted of two granulation-drying cycles per batch. When we tried granulation with the addition of the whole amount of ethanol (400 g) at once, the granules became too pasty to handle. The necessary amount of ethanol (400 g) was determined based on the solubility of NIL (10 g) in ethanol at room temperature. The resulting solid dispersion granules prepared by two granulation-drying cycles were easy to handle and the manufacturing processes was simple, and the subsequent compression and film coating processes were the standard processes. It was thought that this effect resulted from using the ethanolic suspension of MC. To verify this, we prepared an NIL/cl-PVP/MC (1/4/4) solid dispersion by the solvent method with an ethanolic solution of MC. Both the NIL and MC components were dissolved using a 1/1 mixture of ethanol/dichloromethane as the solvent, and the other methods were the same as previously reported.[5] The resulting solid dispersion, as expected, was difficult to grind and handle compared with the ethanolic suspension sample. Hence, our success in the simple manufacturing process reported here was most likely resulted from the use of the ethanolic suspension of MC.

Influence of Grade of cl-PVP cl-PVP has been widely used as a super-disintegrant[6,7] and several grades are commercially available. To investigate the influence of the grade of cl-PVP, we prepared four batches of tablets containing CL, XL, XL-10 or INF-10 as cl-PVP, and MC15 as the commonly used grade of MC. Figure 1 shows the hardness of the core tablets containing various grades of cl-PVP. The hardness increased in proportion to compression load in all four batches, indicating good compressibility of these granules.

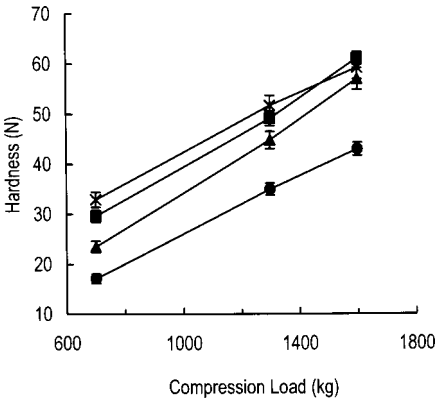

Fig. 1. Compressibility of Core Tablets Containing Various Grades of cl-PVP

●, CL; ▲, XL; ■, XL-10; ×, INF-10.

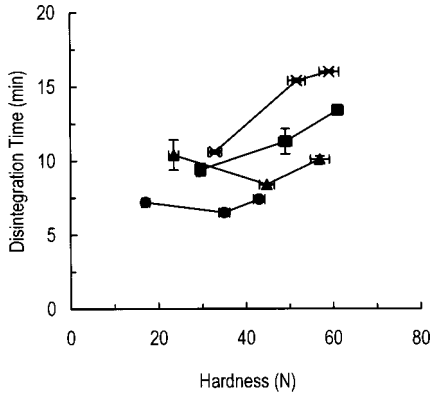

Fig. 2. Relationship between Hardness and Disintegration Time of Core Tablets Containing Various Grades of cl-PVP

●, CL; ▲, XL; ■, XL-10; ×, INF-10.

The tablets containing INF-10 or XL-10 (fine grade) gave higher hardness compared with those containing CL (coarse grade), which was most likely due to an increase of the number of contact points between the particles in a tablet. The mean particle sizes of cl-PVP in the CL, XL, XL-10 and INF-10 grades were 154.8, 126.6, 37.9 and 20.7 μm, respectively.

Figure 2 shows the relationship between hardness and disintegration time of core tablets containing various grades of cl-PVP. The results clearly showed that disintegration time was influenced by hardness and grades of cl-PVP. The tablets containing XL-10 or INF-10 had slow disintegration times compared with those containing CL or XL. In addition, the disintegration time was increased with increasing hardness when using XL-10 or INF-10. On the other hand, the disintegration time was changed little with increasing hardness when using CL or XL. It was reported that coarser grades of cl-PVP enhanced disintegration and dissolution, although hardness was increased by the use of finer grades in tablet formulation,[8] and our results were in agreement with their findings. Therefore, the nature of cl-PVP was not changed by the formation of a solid dispersion and the related manufacturing processes.

Figure 3 shows the dissolution profiles of NIL from film-coated tablets containing various grades of cl-PVP, and the core tablets for each of four batches obtained at the compres-

sion load of 1300 kg. The dissolution profiles of these tablets reached a constant value, except in the case of INF-10, within 60 min, and the fastest dissolution rate was observed for CL and the slowest for INF-10. Our goal is to obtain an increased dissolution tablet, which has a higher solubility and dissolution rate. Therefore, we discuss about solubility and dissolution rate.

Percent dissolution of NIL at 60 min (D60), as an indication of apparent solubility, was obtained from Fig. 3. The D60 values of CL, XL, XL-10 and INF-10 were 75.5, 86.9, 95.5 and 91.1%, respectively, and D60 was increased with decreasing particle size of cl-PVP. The dissolution properties of a drug loading system using various grades of cl-PVP were reported, and the results showed that the dissolution of the drug was influenced by the physical state of the drug and the specific surface area of cl-PVP.[9] Therefore, to investigate the crystallinity of NIL in the CL, we prepared NIL/CL (1/4) solid dispersion by the solvent method, and performed powder X-ray diffraction and differential scanning calorimetry (DSC) by the previously reported methods.[5] The resulting solid dispersion showed a halo in the powder X-ray diffraction and no melting peak in the DSC (data not shown), indicating that NIL was present in an amorphous state. This result suggested that NIL would be present in an amorphous state in the NIL/cl-PVP (1/4) solid dispersions regardless of the particle size of cl-PVP. Therefore, NIL might to be present in an amorphous state in these four batches of tablets. We assumed the reason for the increased D60 with finer grades of cl-PVP such as XL-10 and INF-10 was due to increased dispersibility of NIL in cl-PVP because small particles possess a large specific surface area. In addition, the D60 of INF-10 was smaller than that of XL-10. The dissolution curve of INF-10 was still increasing at 60 min, as shown in Fig. 3. In contrast, the D60 of CL showed lowest value thought to be poor dispersibility of NIL because of a small specific surface area of cl-PVP, and the use of CL as dispersion carrier was not preferred from the point of solubility compared with other grades of cl-PVP.

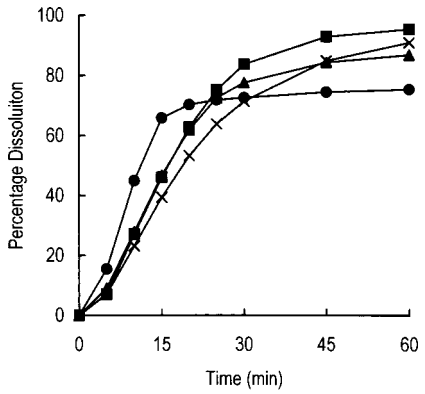

Fig. 3. Dissolution Profiles of NIL from Film-Coated Tablets Containing Various Grades of cl-PVP

●, CL; ▲, XL; ■, XL-10; ×, INF-10. Each core tablet was compressed at 1300 kg.

Table 1 shows the relationship between disintegration time and the time corresponding to 60% dissolution of the NIL (T60) of the film-coated tablets. The T60 values, as an indication of apparent dissolution rate, were obtained from Fig. 3. The disintegration time was found to be related to T60: faster disintegration time gave a faster dissolution rate. This result indicated that the dissolution rate of NIL from tablets was greatly influenced by the disintegration time of the tablets, and the disintegration step was considered to be the rate-determining step for the dissolution of NIL from the tablet dosage form. Consequently, it was thought that the immediately dissolved tablet containing solid dispersion underwent faster disintegration.

Influence of Grade of MC To investigate the influence of the grade of MC, we prepared two batches of tablets containing MC25 as MC, and XL or XL-10 as cl-PVP. The tablet properties, such as hardness, disintegration and dissolution, were compared with those of two batches of tablets containing MC15 and are listed in Table 2. MC25 gave increased hardness and decreased disintegration time compared with MC15. This might be attributed to higher viscosity grade of MC can act both as a binding agent and as a disintegrant for tablet formulation compared with lower grade. In practice, MC is used as a disintegrant for tablets in direct compression.[10] Moreover, MC25 gave a decrease of T60, and D60 was almost the same for tablets containing MC25 and MC15. This indicates that the improvement of dissolution rate by the use of MC25 was due to a decrease of the disintegration time.

Chemical Stability The chemical stability of six batches of tablets containing different grades of cl-PVP or MC was tested at 40 °C, 75% R.H. for six months and the results are listed in Table 3. All six batches showed more than 97 percent residual values during storage, indicating good chemical stability. Therefore, the formulation and manufacturing

Table 1. Disintegration Time and Time Corresponding to 60% Dissolution of the NIL (T60) of Film-Coated Tablets

cl-PVP	MC	Disintegration time (min)	T60 (min)
CL	MC15	9.1	13.6
XL	MC15	12.7	19.4
XL-10	MC15	16.1	19.2
INF-10	MC15	20.1	23.2

Table 2. Properties of Tablets with Compression Load of 1300 kg

cl-PVP	MC	Hardness[a] (N)	Disintegration time (min)		T60[b] (min)	D60[b] (%)
			Core tablet	Film-coated tablet		
XL	MC15	44.8	8.4	12.7	19.4	86.9
XL	MC25	52.0	7.1	10.5	14.9	84.5
XL-10	MC15	49.1	11.3	16.1	19.2	95.5
XL-10	MC25	58.1	9.3	14.9	14.3	95.2

a) Core tablet, *b*) film-coated tablet.

processes used here were considered to be suitable and the grades of cl-PVP and MC did not affect to the chemical stability of NIL.

Physical Stability We established a specification of dissolution: NIL should be dissolved more than 85% at 30 min. To meet this specification, immediately dissolution and higher solubility were required. We selected a formulation containing XL-10 and MC25 as the dispersion carriers, and the tablet stored at 40 °C, 75% R.H. for six months and the results of dissolution test ($n=6$) at each storage period are listed in Table 4. Mean and minimum percent of dissolution showed more than 90 and 89%, respectively in all storage period for six months. The results met our specification indicated that solubility and dissolution rate were stable in during storage. Therefore, NIL might to be present in an amorphous state during storage as well as initial.

Conclusions

NIL solid dispersion granules containing cl-PVP and MC as dispersion carriers could easily be prepared by the agitation granulation method. As the particle size of cl-PVP decreased, hardness and apparent solubility were increased, while the dissolution rate was decreased. With the use of a higher viscosity grade of MC, the hardness and dissolution rate were increased, and apparent solubility did not change. The disintegration time was related to dissolution rate, and therefore the disintegration step was considered to be the rate-determining step for dissolution of NIL solid dispersion tablets. Moreover, the NIL solid dispersion tablets showed good chemical stability. Finally, we obtained enhanced dissolution NIL tablets, which showed a higher dissolution rate and better apparent solubility, by using XL-10 and MC25 as the grades of cl-PVP and MC, respectively. This formulation tablets showed higher solubility and dissolution rate during storage as well as initial indicating good physical stability.

Table 3. Residual Percentage of NIL in Film-Coated Tablets Stored at 40 °C, 75% R.H.

cl-PVP	MC	Storage period			
		Initial	1 month	3 months	6 months
CL	MC15	100.0	100.4	99.0	99.0
XL	MC15	100.0	100.2	101.3	100.4
XL-10	MC15	100.0	99.1	97.2	97.7
INF-10	MC15	100.0	98.9	98.0	97.2
XL	MC25	100.0	101.3	98.5	98.1
XL-10	MC25	100.0	97.8	97.4	97.9

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Table 4. Dissolution Stability of NIL Solid Dispersion Film-Coated Tablets Using XL-10 and MC25 as the Grades of cl-PVP and MC, Respectively

Percent dissolution of NIL at 30 min	Storage period			
	Initial	1 month	3 months	6 months
Mean±S.D.	91.0±1.9	90.1±0.6	91.4±0.8	93.7±2.5
Maximum	94.1	90.9	92.3	97.5
Minimum	89.0	89.2	90.4	90.1

Stored at 40 °C, 75% R.H.