MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 9, pp. 997–1004, 2003

RESEARCH PAPER

An Attempt to Stabilize Nilvadipine Solid Dispersion by the Use of Ternary Systems

Noriyuki Hirasawa,[1,*] Sayoko Ishise,[1] Hitomi Miyata,[1] and Kazumi Danjo[2]

[1]Medicinal Research Department, Nichi-iko Pharmaceutical Co., Ltd., Namerikawa, Japan
[2]Faculty of Pharmacy, Meijo University, Tenpaku-ku, Nagoya, Japan

ABSTRACT

Firstly, we investigated the physical stability of nilvadipine (NIL)/crospovidone (cl-PVP) solid dispersion during storage (40°C, 75% relative humidity) with powder x-ray diffraction, differential scanning calorimetry (DSC) and dissolution test. These studies indicated that recrystallization occurred during storage and that the dissolution of NIL greatly decreased, compared with that of the initial finding. Secondly, to improve the amorphous form physical stability of NIL, methylcellulose (MC) was added to NIL/cl-PVP solid dispersions as a dispersion carrier and NIL/cl-PVP/MC ternary solid dispersion systems were obtained by the solvent method. Powder x-ray diffraction and DSC studies indicated that the amorphous form physical stability of NIL clearly improved in the NIL/cl-PVP/MC solid dispersion systems during storage. Moreover, the dissolution properties of NIL/cl-PVP/MC solid dispersion systems were characterized by cl-PVP markedly enhancing the dissolution of NIL and MC inhibiting the change of the dissolution of NIL during storage. Finally, we obtained an ideal solid dispersion that was accompanied by a consistently higher rate of dissolution.

INTRODUCTION

The solid dispersion technique can be used to improve the dissolution of poorly water-soluble drugs, of which numerous studies have been reported.[1,2] However, there are very few marketed products using this technique because of dissolution stability and manufacturing difficulties.[3,4] Dissolution stability is a significant problem in developing drugs because it is a critical parameter from the standpoint of quality control, regulatory compliance, and impact on the bioavailability of the

*Correspondence: Noriyuki Hirasawa, Medicinal Research Department, Nichi-iko Pharmaceutical Co., Ltd., 205-1 Shimoumezawa, Namerikawa, 936-0857, Japan; Fax: +81-76-475-5530; E-mail: n-hirasawa@nichiiko.co.jp.

DOI: 10.1081/DDC-120025456
0363-9045 (Print); 1520-5762 (Online)

product.[5] Many solid dispersion systems contain amorphous or molecularly dispersed drugs that are often susceptible to changes during storage.[6] It is said that temperature and humidity influence the amorphous state during storage.[7,8] We think the solid dispersion technique would be use widely for commercially product by research of the physical stabilization.

Previously, we reported that the dissolution of nilvadipine (NIL), a poorly water-soluble drug, was improved markedly by the use of crospovidone (cl-PVP) as a dispersion carrier.[9] The aim of this study is to obtain an ideal solid dispersion that is accompanied by a consistently higher rate of dissolution. First, we investigated the amorphous form physical stability of NIL during storage, and it was revealed that recrystallization of NIL occurred. Therefore, in an attempt to stabilize the amorphous form of NIL during storage, methylcellulose (MC) was added to NIL/cl-PVP solid dispersion systems, and NIL/cl-PVP/MC solid dispersion systems were obtained. The ternary solid dispersion systems were evaluated by crystallinity and dissolution studies.

EXPERIMENTAL

Materials

Nilvadipine (Sagami Chemical Industry, Japan), cl-PVP (KollidonCL-M; BASF Japan, Japan), MC (Metolose SM-15; Sin-Etsu Chemical, Japan), hydroxypropyl cellulose (HPC, HPC-L; Nippon Soda, Japan), hydroxypropylmethylcellulose (HPMC, TC-5RW; Sin-Etsu Chemical, Japan), carmellose (CMC, NS-300; Gotoku Chemical, Japan), carmellose calcium (CMC-Ca, ECG-505; Gotoku Chemical, Japan), croscarmellose sodium (cl-CMC-Na, Ac-Di-Sol; Asahi Kasei, Japan), hydroxyethylcellulose (HEC, SE-400; Daicel Chemical Industries, Japan), low-substituted hydroxypropyl cellulose (L-HPC, LH-22; Sin-Etsu Chemical, Japan), and microcrystalline cellulose (MCC, Avicel 101; Asahi Kasei, Japan) were used in this study. Other chemicals used were of reagent grade.

Preparation of Solid Dispersions

Solid dispersions at various weight ratios were prepared by the solvent method. One gram of NIL was dissolved in 100 g of ethanol, and then various amounts of carriers, except HPC, were suspended in this solution because these carriers were insoluble in ethanol. Hydroxypropyl cellulose was soluble in ethanol alone and was dissolved with NIL. The solvent was evaporated under reduced pressure at 45°C and then dried almost completely in a vacuum desiccator for 12 hr. The solid sample was ground gently with a mortar and pestle and passed through an 180 μm sieve.

Preparation of Physical Mixtures

Physical mixtures were prepared by mixing NIL and the carrier with a test-tube mixer (Vortex-Genie2; Scientific Industries, Japan) for 5 min. The samples were passed through an 180 μm sieve prior to use.

Powder X-ray Diffraction

Powder x-ray diffraction analysis was performed with an x-ray diffractometer (RU-200BV; Rigaku, Japan). The operating conditions were as follows: target, CuKα; voltage, 40 kV; current, 80 mA; and scan speed, 5°/min.

Thermal Analysis

Thermal analysis was carried out by differential scanning calorimetry (DSC) with a type DSC7 apparatus (Perkin Elmer). Samples were placed in sealed aluminum pans and scanned at a heating rate of 10°C/min in a nitrogen atmosphere.

Dissolution Test

Dissolution tests were performed according to the JP14 paddle method. Sample powder, including 10 mg of NIL was put into the dissolution medium (900 mL 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, Japan) at 242 nm.

Stability Test

Stability tests were performed as follows: solid dispersions were stored in an open glass bottle at 40°C, 75% relative humidity (RH).

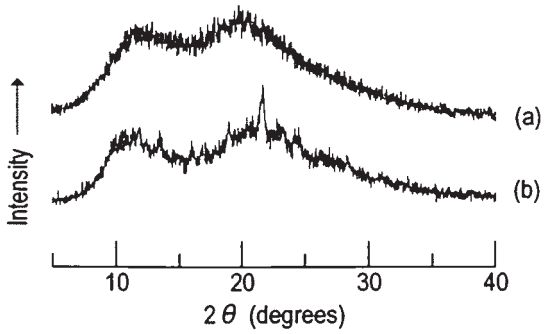

Figure 1. Powder x-ray diffraction patterns of NIL/cl-PVP (1/4) solid dispersion during storage at 40°C, 75% RH. (a), Initial; (b), After storage (4 weeks).

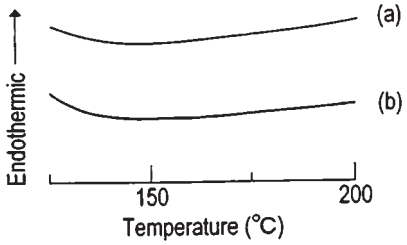

Figure 2. DSC thermograms of NIL/cl-PVP (1/4) solid dispersion during storage at 40°C, 75% RH. (a), Initial; (b), After storage (4 weeks).

RESULTS AND DISCUSSION

Amorphous Form Stability of NIL in the NIL/cl-PVP Solid Dispersion

To investigate the amorphous form stability of NIL during storage in the NIL/cl-PVP solid dispersion systems, powder x-ray diffraction and DSC analysis were used. Powder x-ray diffraction patterns and DSC thermograms of NIL/cl-PVP (1/4) solid dispersion initially and after 4 weeks of storage, are shown in Figs. 1 and 2, respectively. Nilvadipine was present in an amorphous form initially,[9] but powder x-ray diffraction after 4 weeks of storage (Fig. 1b) showed many sharp diffraction peaks, indicating that recrystallization of NIL had occurred during storage. Imaizumi et al. also reported physical instability of an indomethacin/cl-PVP solid dispersion system in the presence of moisture, though the system is stable to temperature alone.[10] However, DSC thermograms of the solid dispersions were similar both initially and after 4 weeks of storage (Fig. 2). Similar discrepant results also were observed in other drug/carrier systems,[11,12] in which powder x-ray diffraction showed sharp diffraction peaks. However, DSC shows no melting peak of the drug, and the reason for these observations is not clear. In conclusion, it was obvious that the recrystallization of NIL occurred during storage at 40°C, 75% RH for 4 weeks in the NIL/cl-PVP solid dispersion systems.

Effects of NIL/cl-PVP/MC Ternary Solid Dispersion Systems on the Amorphous Form Stability of NIL

To improve the amorphous form stability of NIL during storage, MC was added to the NIL/cl-PVP solid dispersion systems as a dispersion carrier, and NIL/cl-PVP/MC ternary solid dispersion systems were obtained by the solvent method. The effects of MC on the crystallinity of NIL initially and after 4 weeks of storage were studied, and their powder x-ray diffraction patterns and DSC thermograms are shown in Figs. 3 and 4, respectively. Initially, all solid dispersions showed a halo (Fig. 3) and no melting peak of NIL (Fig. 4), indicating that NIL was present in an amorphous form. After 4 weeks of storage, solid dispersions containing 0.5 or 1 of MC showed sharp diffraction peaks due to the crystallization of NIL, while those containing 2 or 4 of MC showed a halo (Fig. 3). However, all solid dispersions showed no melting peak of NIL (Fig. 4). These observations indicated that MC inhibited the recrystallization of NIL during storage.

The effects of cl-PVP on the crystallinity of NIL initially and after 4 weeks of storage were studied, and their powder x-ray diffraction patterns and DSC thermograms are shown in Figs. 5 and 6, respectively. Initially, all solid dispersions showed a halo (Fig. 5) and no melting peak of NIL (Fig. 6), indicating that NIL was present in an amorphous form. After 4 weeks of storage all solid dispersions still showed a halo (Fig. 5). However, solid dispersions containing 0.5 or 1 of cl-PVP showed a melting peak of NIL (Fig. 6). In addition, NIL/MC (1/4) binary solid dispersion also showed a melting peak of NIL both initially and after 4 weeks of storage. On the other hand, NIL/cl-PVP (1/4) binary solid dispersion showed no melting peak of NIL both initially or after 4 weeks of storage as described above. These results indicated that the appearance of a melting peak of NIL in DSC was characteristic of NIL/MC solid dispersions. Hence, it suggested that solid dispersions were formed mainly between NIL and

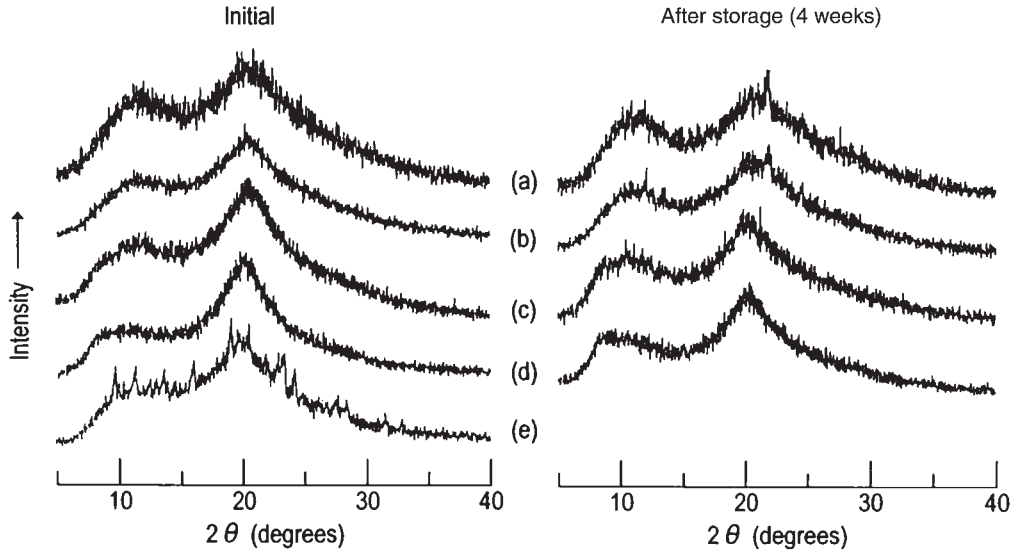

Figure 3. Effects of MC on powder x-ray diffraction patterns of NIL/cl-PVP/MC solid dispersion systems during storage at 40°C, 75% RH. (a), 1/4/0.5 SD; (b), 1/4/1 SD; (c), 1/4/2 SD; (d), 1/4/4 SD; (e), 1/4/4PM. SD = solid dispersion; PM = physical mixture.

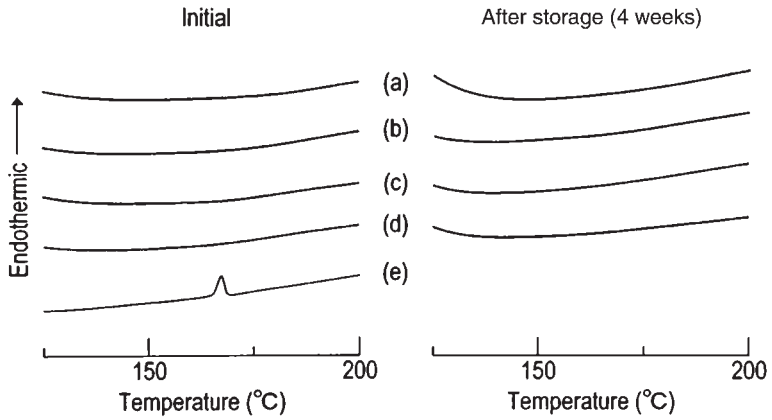

Figure 4. Effects of MC on DSC thermograms of NIL/cl-PVP/MC solid dispersion systems during storage at 40°C, 75% RH. (a), 1/4/0.5 SD; (b), 1/4/1 SD; (c), 1/4/2 SD; (d), 1/4/4 SD; (e), 1/4/4 PM. SD = solid dispersion; PM = physical mixture.

cl-PVP initially, but were formed mainly between NIL and MC after storage when the ternary solid dispersions contained 0.5 or 1 of cl-PVP.

Dissolution Properties of NIL from NIL/cl-PVP/MC Solid Dispersion Systems During Storage

To investigate the dissolution properties of NIL from solid dispersions during storage, dissolution tests were examined. The effects of MC on the dissolution of solid dispersions during storage are shown in Fig. 7. Initially, all solid dispersions containing MC showed similar dissolution profiles and their supersaturate concentration continued for a long time. On the other hand, the supersaturate concentration of NIL/cl-PVP (1/4) binary solid dispersion decreased after 3 hr, most likely due to the recrystallization of NIL.[9] These phenomena were attributed to the MC-inhibited recrystallization of the drug from the supersaturate concentration. Hasegawa et al. reported that more hydrophobic water-soluble polymer such as MC and HPMC could inhibit recrystallization from supersaturate concentration, and they concluded the inhibition

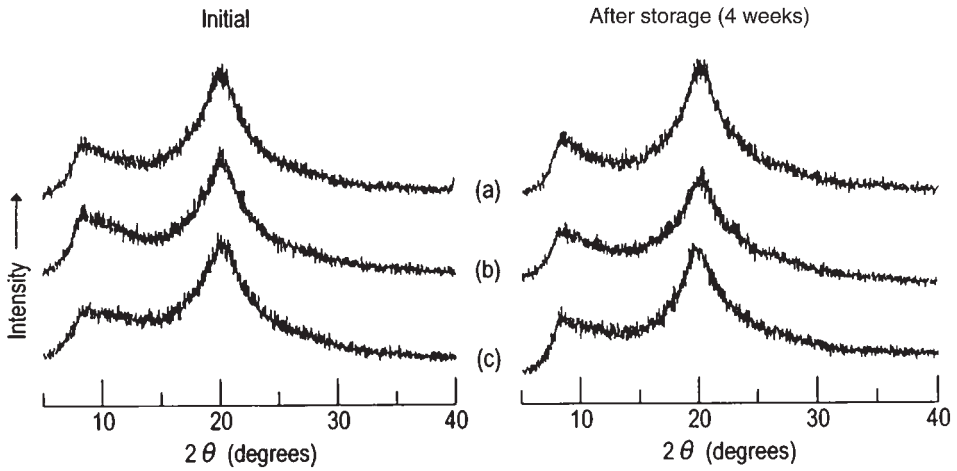

Figure 5. Effects of cl-PVP on powder x-ray diffraction patterns of NIL/cl-PVP/MC solid dispersion systems during storage at 40°C, 75% RH. (a), 1/0.5/4 SD; (b), 1/1/4 SD; (c), 1/2/4 SD. SD = solid dispersion.

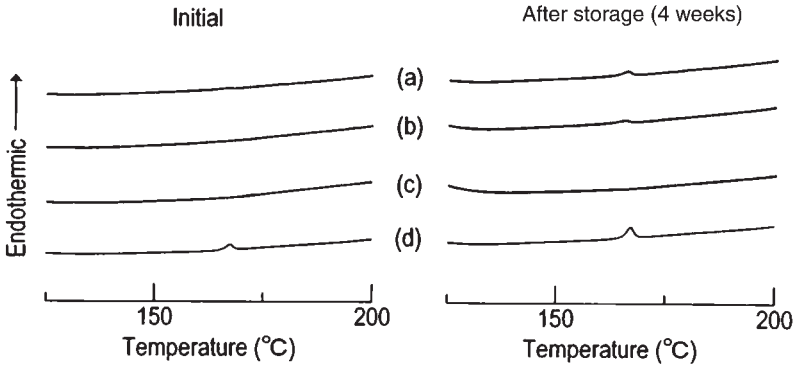

Figure 6. Effects of cl-PVP on DSC thermograms of NIL/cl-PVP/MC solid dispersion systems during storage at 40°C, 75% RH. (a), 1/0.5/4 SD; (b), 1/1/4 SD; (c), 1/2/4 SD; (d), 1/0/4 SD. SD = solid dispersion.

mechanism was attributed to the crystal growth process that was inhibited by a physicochemical interaction between the polymer and the surface of drug crystal.[12] After 4 weeks of storage, the dissolution of the NIL/cl-PVP binary solid dispersion fell to its lowest dissolution level, the same as that of the physical mixtures attributed to the recrystallization of NIL occurring during storage.

The effects of cl-PVP on the dissolution of solid dispersions during storage are shown in Fig. 8. Initially, the dissolution of NIL increased in proportion to the content of cl-PVP in the NIL/cl-PVP/MC solid dispersion systems. After 4 weeks of storage, the dissolution changed little compared with that of the initial NIL/MC binary solid dispersion. Figure 9 shows the relationship between the weight ratio of cl-PVP to MC (cl-PVP/MC) and the maximum percentage of dissolution (Dmax) initially and after 2 or 4 weeks of storage in the NIL/ cl-PVP/MC solid dispersion systems. Initially, when the cl-PVP/MC was 1/4 or more, Dmax of solid dispersions showed the same high value regardless of their cl-PVP/MC. After storage, when the cl-PVP/MC was 4/1 or more, Dmax was greatly decreased compared with that of the initial finding. The reason was attributed to the recrystallization of NIL occurring during storage. In addition, when the cl-PVP/MC was 1/4 or less, Dmax was decreased compared with that of the initial finding and seemed to fall to the level of the NIL/MC binary solid dispersion. The reason attributed to the change in the formation of the solid dispersion during storage was as described above; the solid dispersion formed mainly between NIL and cl-PVP initially and formed mainly between NIL and MC after storage, because cl-PVP enhanced the

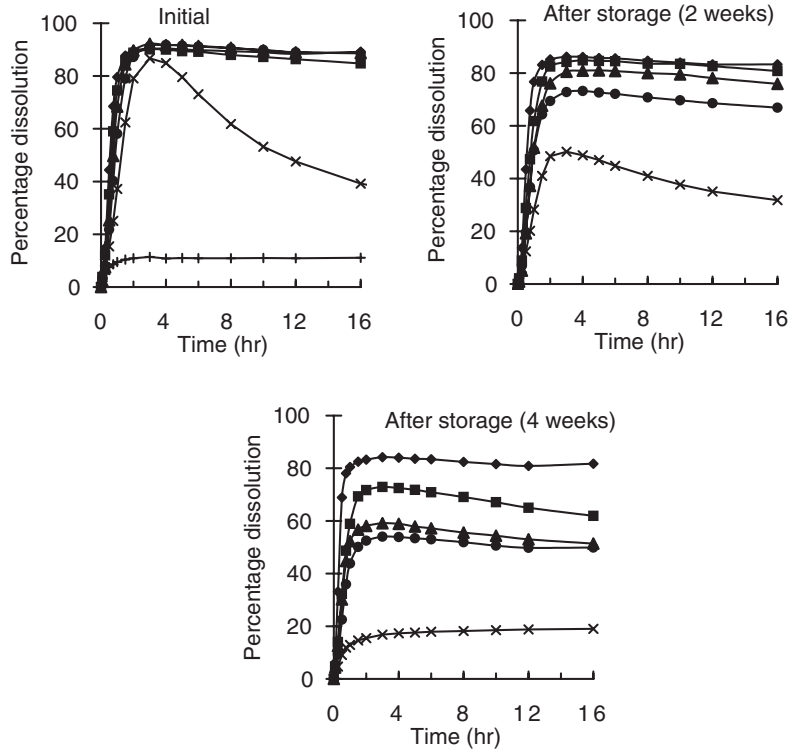

Figure 7. Effects of MC on the dissolution of NIL/cl-PVP/MC solid dispersion systems during storage at 40°C, 75% RH. ●, 1/4/0.5 SD; ▲, 1/4/1 SD; ■, 1/4/2 SD; ◆, 1/4/4 SD; ×, 1/4/0 SD; +, 1/4/4 PM. Each point represents average ($n = 3$). SD = solid dispersion; PM = physical mixture.

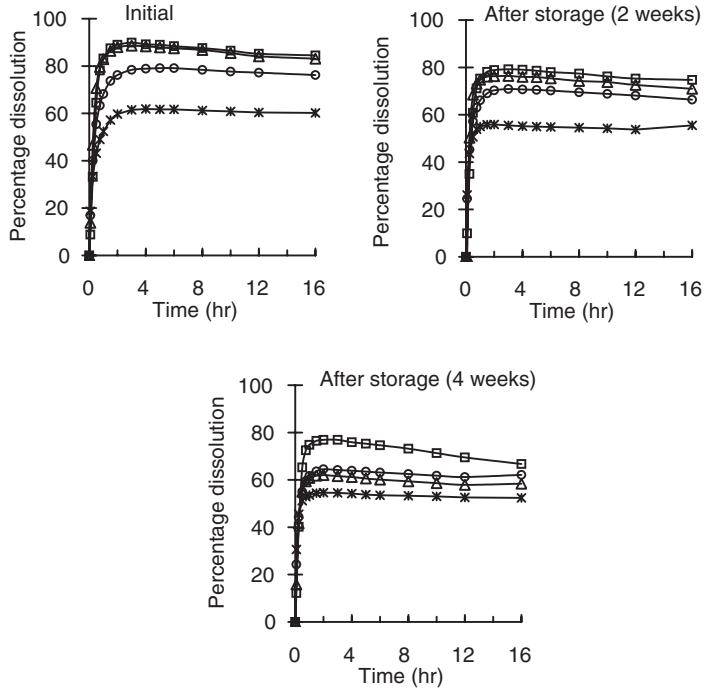

Figure 8. Effects of cl-PVP on the dissolution of NIL/cl-PVP/MC solid dispersion systems during storage at 40°C, 75% RH. ○, 1/0.5/4 SD; △, 1/1/4 SD; □, 1/2/4 SD; *, 1/0/4 SD. Each point represents average ($n = 3$). SD = solid dispersion.

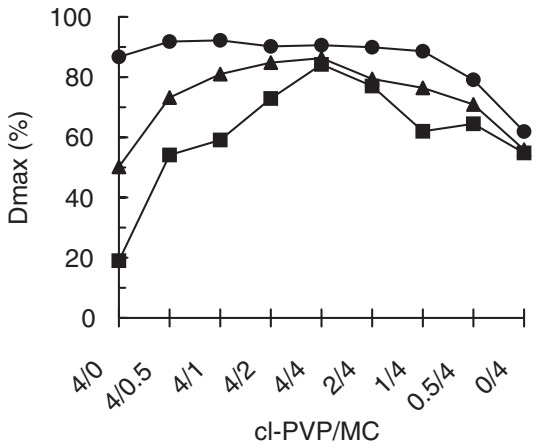

Figure 9. Relationship between the weight ratio of cl-PVP to MC (cl-PVP/MC) and the maximum percentage of dissolution (Dmax) during storage at 40°C, 75% RH. ●, Initial; ▲, After storage (2 weeks); ■, After storage (4 weeks).

Table 1. Maximum percentage of dissolution (Dmax) and percentage of dissolution after 16 hr (D16h) of NIL/cl-PVP/cellulose derivatives (1/4/4) ternary solid dispersions during storage at 40°C, 75% RH.

	Storage period			
	Initial		2 weeks	4 weeks
Cellulose derivatives	Dmax (%)	D16h (%)	Dmax (%)	Dmax (%)
MC	90.6	(89.2)	86.3	84.2
HPC	96.7	(45.4)	22.2	22.5
HPMC	86.7	(85.0)	87.1	85.8
CMC	79.8	(48.4)	—	17.0
CMC-Ca	82.9	(35.5)	—	14.2
cl-CMC-Na	81.1	(34.0)	38.1	23.7
HEC	79.2	(34.3)	18.9	16.8
L-HPC	81.9	(50.5)	42.9	26.7
MCC	81.1	(57.6)	33.5	29.3

dissolution of NIL compared with the use of MC as a dispersion carrier of NIL.

In conclusion, the dissolution properties of NIL/cl-PVP/MC solid dispersion systems were characterized by cl-PVP markedly enhancing the dissolution and MC inhibiting the change of dissolution during storage. The NIL/cl-PVP binary solid dispersion showed high Dmax value, however, it was decreased during storage. The NIL/MC binary solid dispersion showed stable Dmax value during storage, however, it was lower than, binary system with cl-PVP. Finally, the ideal solid dispersion was obtained in the NIL/cl-PVP/MC (1/4/4) solid dispersion.

Several stabilized solid dispersions were obtained in the case of low drug content[14,15] Therefore, various cellulose derivatives were added and NIL/cl-PVP/cellulose derivatives (1/4/4) ternary solid dispersions were obtained. The Dmax of these solid dispersions initially and after 2 or 4 weeks of storage are shown in Table 1. It was shown that MC and HPMC could stabilize the dissolution of NIL during storage compared with the use of other cellulose derivatives. In addition, MC and HPMC showed almost the same value between Dmax and percentage of dissolution after 16 hr (D16h) in initial samples, indicating these polymer could maintain supersaturate concentration for a long time. However, other cellulose derivatives such as HPC, CMC, CMC-Ca, cl-CMC-Na, HEC, L-HPC, and MCC could not inhibit recrystallization form supersaturate concentration, because the D16h values were observed as a much lower value compared with Dmax. The stabilization mechanism could be illustrated as follows: during exposure to high temperature and humidity, a portion of solid dispersion was dissolved in absorbed water, resulting in supersaturate concentration. Methylcellulose and HPMC could maintain supersaturate concentration for a long time, therefore, these polymers could act as a stabilizer. Hence, it was indicated that the stabilization of NIL/cl-PVP solid dispersion systems could be obtained by the addition of a specific dispersion carrier.

CONCLUSIONS

Recrystallization of NIL occurred during storage in the NIL/cl-PVP solid dispersion systems, and the dissolution of NIL greatly decreased compared with that of the initial finding. The amorphous form physical stability of NIL improved by the use of NIL/cl-PVP/MC ternary solid dispersion systems. Moreover, dissolution properties of NIL/cl-PVP/MC solid dispersion systems were characterized by cl-PVP enhancing the dissolution and MC inhibiting the change of dissolution during storage. We obtained an ideal solid dispersion that was accompanied by a consistently higher rate of dissolution in the NIL/cl-PVP/MC (1/4/4) solid dispersion. In addition, HPMC also was useful to stabilize the dissolution of NIL/cl-PVP solid dispersion systems during storage as a dispersion carrier.

ACKNOWLEDGMENT

The authors are grateful to Dr. Mitsugu Ishida, director of Nichi-iko Pharmaceutical, for his helpful advice and useful discussions throughout this work.

REFERENCES

1. Sekiguchi, K.; Obi, N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull. **1961**, *9* (11), 866–872.
2. Ciou, W.L.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. **1971**, *60* (9), 1281–1302.
3. Bloch, D.W.; Speiser, P.P. Solid dispersions—fundamentals and examples. Pharm. Acta Helv. **1987**, *62* (1), 23–27.
4. Serajuddin, A.T.M. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. **1999**, *88* (10), 1058–1066.
5. Murthy, K.S.; Sellassie, I.G. Current perspective on the dissolution stability of solid oral dosage forms. J. Pharm. Sci. **1993**, *82* (2), 113–126.
6. Ford, J.L. The current status of solid dispersions. Pharm. Acta Helv. **1986**, *61* (3), 69–88.
7. Hancock, B.C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. **1997**, *86* (1), 1–12.
8. Sugimoto, I.; Sasaki, K.; Kuchiki, A.; Ishihara, T.; Nakagawa, H. Stability and bioavailability of nifedipine in fine granules. Chem. Pharm. Bull. **1982**, *30* (12), 4479–4488.
9. Hirasawa, N.; Ishise, S.; Miyata, H.; Danjo, K. Physicochemical characterization and drug release studies of nilvadipine solid dispersions using water-insoluble polymer as a carrier. Drug Develop. Ind. Pharm. **2003**, *29* (3), 339–344.
10. Imaizumi, H.; Nambu, N.; Nagai, T. Stabilization of amorphous state of indomethacin by solid dispersion in polyvinypolypyrrolidone. Chem. Pharm. Bull. **1983**, *31* (7), 2510–2512.
11. Tantishaiyakul, V.; Kaewnopparat, N.; Ingkatawornwong, S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30. Int. J. Pharm. **1996**, *143*, 59–66.
12. Yuasa H.; Ozeki T.; Takahashi H.; Kanaya Y.; Ueno, M. Application of the solid dispersion method to the controlled release of medicine. VI. Release mechanism of a slightly water soluble medicine and interaction between flurbiprofen and hydroxypropyl cellulose in solid dispersion. Chem. Pharm. Bull. **1994**, *42* (2), 354–358.
13. Hasegawa, A.; Kawamura, R.; Nakagawa, H.; Sugimoto, I. Dissolution mechanism of solid dispersions of nifedipine with enteric coating agents. Yakugaku Zasshi **1985**, *105* (6), 586–592.
14. Ito, S.; Demachi, M.; Toriumi, Y.; Adachi, T.; Itai, S.; Hirayama, F.; Uekama, K. Improvement of dissolution characteristic of a new chalcone derivative, SU-740: comparison between size reduction, solid dispersion and inclusion complexation. Chem. Pharm. Bull. **1995**, *43* (12), 2221–2225.
15. Ohnishi, N.; Yokoyama, T.; Umeda, T.; Kiyohara, Y.; Kuroda, T.; Kita, Y.; Kuroda, K. Preparation of sustained-release suppositories of indomethacin using a solid dispersion system and evaluation of bioavailability in rabbits. Chem. Pharm. Bull. **1986**, *34* (7), 2999–3004.