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Evaluation of photostability of solid-state nicardipine hydrochloride polymorphs by using Fourier-transformed reflection–absorption infrared spectroscopy – effect of grinding on the photostability of crystal form

Reiko Teraoka*, Makoto Otsuka, Yoshihisa Matsuda

Department of Pharmaceutical Technology, Kobe Pharmaceutical University, Motoyama-Kitamachi 4-19-1, Higashi-Nada, Kobe 658-8558, Japan

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Abstract

Photostability and physicochemical properties of nicardipine hydrochloride polymorphs (α- and β-form) were studied by using Fourier-transformed reflection–absorption infrared spectroscopy (FT-IR-RAS) of the tablets, X-ray powder diffraction analysis, differential scanning calorimetry (DSC), and color difference measurement. It was clear from the results of FT-IR-RAS spectra after irradiation that nicardipine hydrochloride in the solid state decomposed to its pyridine derivative when exposed to light. The photostability of the ground samples of two forms was also measured in the same manner. The two crystalline forms of the drug changed to nearly amorphous form after 150 min grinding in a mixer mill. X-ray powder diffraction patterns of those ground samples showed almost halo patterns. The nicardipine hydrochloride content on the surface of the tablet was determined based on the absorbance at 1700 cm^{-1} attributable to the C=O stretch vibration in FT-IR-RAS spectra before and after irradiation by fluorescent lamp (3500 lx). The photodegradation followed apparently the first-order kinetics for any sample. The apparent photodegradation rate constant of β-form was greater than that of α-form. The ground samples decomposed rapidly under the same light irradiation as compared with the intact crystalline forms. The photodegradation rate constant decreased with increase of the heat of fusion.

Keywords: Nicardipine hydrochloride; Photostability; Fourier-transformed reflection–absorption infrared spectroscopy; Crystal form; Solid state

1. Introduction

It is essential to evaluate the photostability of intact drug in preformulation stage of the process of photo-

* Corresponding author. Tel.: +81 78 441 7531; fax: +81 78 441 7532.
E-mail address: teraoka@kobepharma-u.ac.jp (R. Teraoka).

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labile dosage form development. Many investigators have demonstrated the light stability of dihydropyridine analogs in solution. The position of the nitro substitution produced differences in the photostability of the compounds studied and stability studies of the compounds in buffered solutions (pH 7) stored under room light conditions showed that only the ortho-derivative was unstable (Sturm et al., 2001). The effects of the solvent (ethanol, acetone, dichloromethane), drug concentration and radiation wavelength on the lacidipine photostability were evaluated and the cis-isomer and a photocyclic isomer proved to be the main photodegradation products (De Filippis et al., 2002). Photodegradation of nilvadipine was carried out under the conditions recommended in the first version of the document issued by the International Conference on Harmonization (ICH), currently in force in the studies of photochemical stability of drugs (Augustyniak et al., 2001; Mielcarek et al., 2000). In addition, there have been several reports (Akimoto et al., 1988; Binda and Dondi, 1981; Ebel et al., 1978; Thoma and Klimek, 1985) dealing with the photodegradation of nifedipine in solution. However, there are few reports (De Villiers et al., 1992; Matsuda et al., 1994; Matsuda and Tatsumi, 1990; Qin and Frech, 2001; Teraoka et al., 1999) on the effect of crystal and amorphous forms of drug photostability because the topochemical photodegradation in the solid state was influenced by the particle size and, consequently, it is very difficult to establish the reproducible experimental conditions.

Nicardipine hydrochloride (2-(*N*-benzyl-*N*-methylamino) ethyl methyl (RS)-1, 4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3, 5-pyridinedicarboxylate monohydrochloride) is an effective calcium antagonist and has been widely used for the treatment of coronary heart disease. The drug is commercially available in injections, tablets, and powders. Although its stability in injectable solutions have been reported (Baaske et al., 1996; Bonferoni, 1992), the photostability in the solid state has not been established to date.

Nicardipine hydrochloride was isolated by Iwatani et al. (1979) in two crystalline forms and the two crystalline forms were characterized by Yan and Giunchedi (1990). Qin and Frech (2001) reported that the photodegradation rate of the amorphous MK-912 was approximately 40 times faster than that of the crystalline MK-912 under the photostability test conditions of the ICH guidelines.

Grinding is often carried out to reduce the particle size of the intact drug. However, not only desired changes in physical properties such as specific surface area and shape, but also changes in physicochemical properties such as catalytic activity can take place during grinding, and consequently polymorphic transformation or conversion to amorphous form may occur. Kitamura et al. (1989) reported that the ground cefixime crystals showed an increase in the apparent discoloration rate constant with the increase in the grinding time.

The photodegradation of drug in the solid state is a topochemical reaction, and therefore, it is not appropriate to evaluate the decomposition ratio by conventional analytical methods such as HPLC, UV, and IR spectroscopy. Fourier-transform infrared reflection–absorption spectroscopy (FT-IR-RAS) allows pure materials to be analyzed without addition of KBr (Golden, 1985). Recently, photostability of carbamazepine polymorphs (Matsuda et al., 1994) and nifedipine (Teraoka et al., 1999) was investigated by using FT-IR-RAS. Therefore, we used FT-IR-RAS to measure pure materials using nicardipine hydrochloride tablets. The purpose of the present study was to evaluate the photodegradation of crystalline and ground nicardipine hydrochloride by using a simple and fast FT-IR-RAS method for quantitative determination of the drug.

2. Materials and methods

2.1. Materials

Bulk nicardipine hydrochloride powder (α- and β-forms) was kindly supplied Yamanouchi Ltd. Japan and those samples were used without purification. The commercial solvents for HPLC analysis were used without further purification.

2.2. Mechanical treatment

The drug powder was ground for 150 min in a 10 mL agate vessel by vibrating-type mixer mill (model MM2, Retsch Co., Germany), containing agate ball (the diameter and number of ball was 12 mm × 1) at 25 °C.

2.3. Preparation of sample pellets

The accurately weighed intact and ground nicardipine hydrochloride powders of two crystal forms

(500 mg) were compressed using an accurate compression/tension testing machine (Autograph model IS-5000, Shimadzu Co., Kyoto, Japan) equipped with flat-faced punches and a cylindrical die (20 mm i.d.) set at a compression speed of 15 mm/min at 9.8 kPa, and then the pellet of ca. 1.5 mm in thickness was prepared. The variation in thickness of these pellets was negligible among two forms and amorphous forms, thus suggesting that the surface morphology of these pellets was almost the same.

2.4. Irradiation test

Sample pellets were stored in a light-irradiation tester (Light-Tron LT-120, Nagano Science Co., Takatsuki, Japan) equipped with a white fluorescent lamp (rapid-start type 20 W). The illuminance was set at 3500 lx. The irradiation tests were carried out at 25 °C and 0% relative humidity.

2.5. X-ray powder diffraction analysis

X-ray powder diffraction patterns were measured by an X-ray diffractometer (XD-3A, Shimadzu Co., Kyoto, Japan) at room temperature. The operating conditions were as follows: Target, Cu; filter, Ni; voltage, 30 kV; current, 15 mA; receiving slit, 0.1 mm; time constant, 1 s; scanning speed, 4° 2θ/min.

2.6. FT-IR-RAS measurement

FT-IR spectra of the sample pellets were obtained by FT-IR-RAS on an FT-IR spectrometer (model FT-IR 1600, Perkin Elmer Co., Yokohama, Japan) and modified by using the Kramers-Krönig equation. The spectral data were not transformed by the normalized function.

2.7. Colorimetric measurement

The surface color of the compressed sample pellet was measured with an integrating sphere-type color difference meter (model ND-300A, Nippon Denshoku Co., Tokyo, Japan) after the designated irradiation times. The color difference ($\triangle E$) before and after irradiation was calculated to evaluate the degree of discoloration (Matsuda et al., 1989). All values were the averages of two measurements.

2.8. Photodiode array procedures for nicardipine hydrochloride

The photodiode array for nicardipine hydrochloride after storage was carried out by an HPLC system (Waters) equipped with a photodiode array detector (Waters, model 991J); the prepacked column (LiChrospher 100 CN (5 μm), 15 cm × 4.0 mm, Merck, Japan) was operated at room temperature at a flow rate of 0.7 mL/min. The mobile phase was composed of a mixture of 0.01 M sodium phosphate buffer (pH 6.1) and acetonitrile (1:1 v:v). After irradiation, the surface of the pellet was scraped off and dissolved in methanol. Subsequently the solution was analyzed by the above HPLC system.

2.9. Thermal analysis

The thermograms of the two crystal forms and the ground powders were recorded on a differential scanning calorimetry (DSC) (model 3100, Mac Science Co., Tokyo, Japan). The operating conditions in the open-pan system were as follows: sample weight, 5 mg; heating rate, 180 °C/min; N_2 gas flow rate, 50 mL/min.

3. Results and discussion

3.1. Grinding of α- and β-forms of nicardipine hydrochloride

Fig. 1 shows the X-ray powder diffraction patterns of the intact crystals of nicardipine hydrochloride and 150 min ground samples. These crystals exhibit characteristic patterns and the X-ray powder diffraction patterns of α- and β-forms were confirmed to be the same as those reported by Yan and Giunchedi (1990). The diffraction peak intensities of two forms decreased after grinding and X-ray powder diffraction patterns of the two forms ground for 150 min showed almost halo patterns. This suggests that most of α and β-forms converted into amorphous state.

The thermal profiles of nicardipine hydrochloride modifications are shown in Fig. 2. The α- and β-forms had an endothermic peak due to fusion at 188.7 °C and 171.1 °C, respectively. After 150 min of grinding in mixer mill, the temperature of both endothermic peaks became lower and α-form showed an exothermic peak

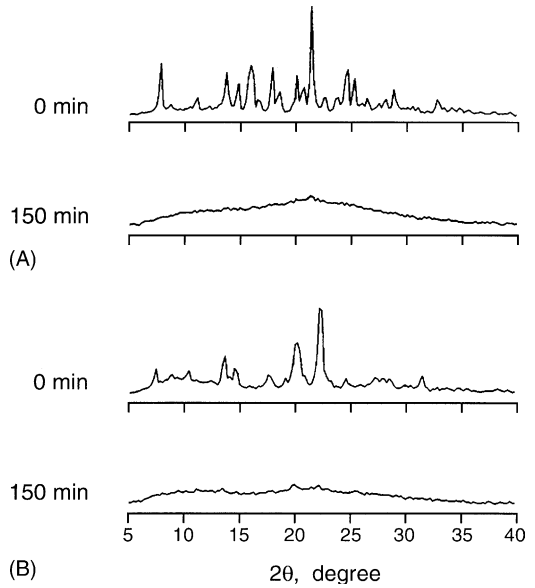

Fig. 1. Changes in X-ray powder diffraction patterns of nicardipine hydrochloride polymorphs after grinding: (A) α-form; (B) β-form.

at 150 °C due to crystallization, and then an endothermic peak at 181.2 °C due to fusion. On the other hand, the ground β-form sample showed no exothermic peak and exhibited a weak endothermic peak at 163.8 °C due to fusion, suggesting that the ground β-form was higher amorphism compared with the ground α-form. That is to say, the ground β-form has a greater degree of disorder of the molecular arrangement. X-ray powder diffraction profiles of both ground powders had no change and showed almost halo patterns when these powders were stored at 25° in a desiccator with phosphorus pentoxide for two weeks. This result suggests that these amorphous powders were stable and crystallization did not occur under low humidity. Therefore, light stability test was performed in the closed box which put transparent quartz glass in the window and was maintained at low humidity with phosphorus pentoxide.

3.2. Photodegradation product

Fig. 3 shows the chromatograms resulting from the HPLC analysis of the powder scraped from tablet surface after irradiation under the white fluorescent lamp at 3500 lx. The two peaks were detected at 260 nm after irradiation, and a new peak at 4.2 min appeared as a result of photochemical reaction in addition to nicardipine hydrochloride at 5.3 min. The UV spectra corresponding to these peaks were obtained by photodiode array technique (Fig. 3) and peaks a and b exhibited λ_{max} of the UV spectra at 237 nm and between 250 and 290 nm, respectively. Photostability of nicardipine hydrochloride solution under both UV and daylight conditions was reported by Bonferoni et al. (1992). They reported that nicardipine hydrochloride was light-sensitive and the drug gave rise to the pyridine derivative by the photodegradation. As compared with their results of UV spectra obtained by photodiode array method, the peak b indicated to be the pyridine derivative of nicardipine hydrochloride. It was clear that nicardipine hydrochloride was degraded in the solid state as well as in the solution under white fluorescent lamp.

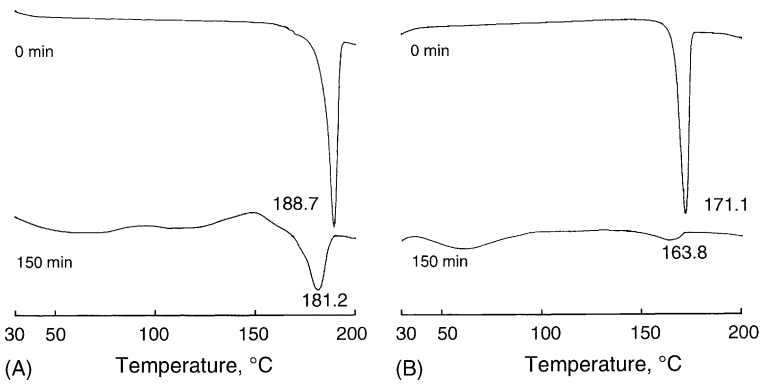

Fig. 2. Changes in DSC curves of nicardipine hydrochloride polymorphs after grinding: (A) α-form; (B) β-form.

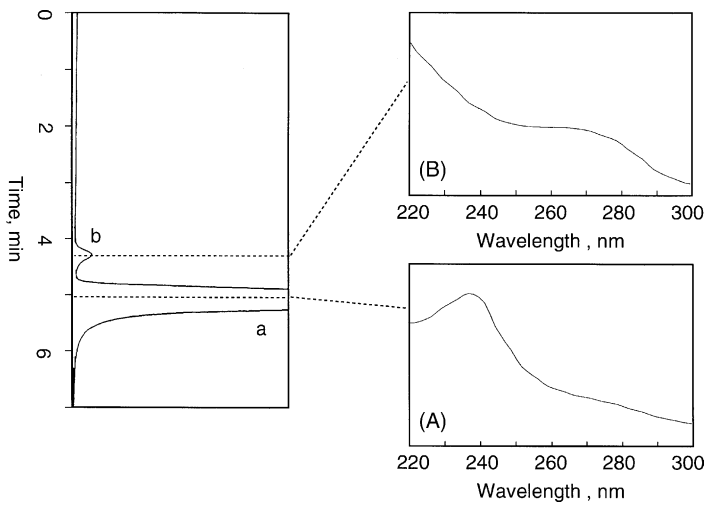

Fig. 3. The results detected by photodiode-array for unknown degradation product (b) and intact nicardipine (a).

3.3. Appearance change in polymorphs of nicardipine hydrochloride

Fig. 4 shows the time courses for discoloration of nicardipine hydrochloride under the white fluorescent lamp at 25 °C and 0%RH. The surface color of all tablets prepared from the two crystalline forms and the ground samples turned gradually from light yellow to orange-yellow upon exposure to light. The color change of all tablets became more intense with increasing irradiation time. The tablets of α-form ground samples were easy to discolor as compared with tablets of the crystals, whereas the $\triangle E$ value of β-form was greater than α-form after 13-d irradiation. As we have already reported on the discoloration of nifedipine tablet (Teraoka et al., 1999), the surface of nifedipine tablet also turned gradually from fresh yellow to dark yellow upon exposure to light by mercury vapor and fluorescent lamps. This suggests that such 1,4-dihydropyridine derivatives are susceptible to photodegradation. There are few reports with respect to photostability of modifications. Matsuda and Tatsumi (1990) reported that distinctly different degree of physicochemical photostability (coloration) was evident among the modifications of furosemide and the stable form did not show significant coloration even when irradiated with intense light. The solid-state photolytic degradation of two polymorphic forms of furosemide was investigated by De Villiers et al. (1992). Form I was photochemically more stable than form II, especially under a nitrogen atmosphere.

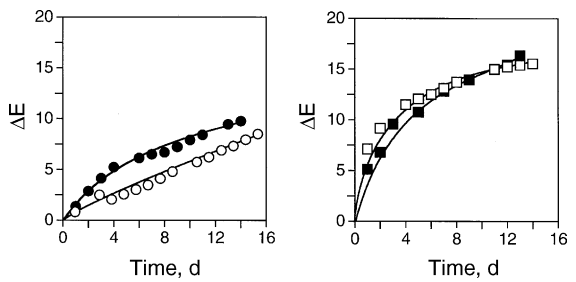

Fig. 4. Changes in color difference ($\triangle E$) of α- (◯,●) and β- (□,■) forms of nicardipine hydrochloride before and after grinding. The open and closed symbols represent the intact and ground powder after 150 min, respectively.

The surface of carbamazepine pellets turned gradually from white to yellow-orange upon exposure to light for all crystalline forms, and the discoloration rate of form II was faster than that of forms I and III (Matsuda et al., 1994).

3.4. Evaluation of photodegradation on the surface of nicardipine hydrochloride tablets

Fig. 5 shows the FT-IR-RAS spectra of β-form of nicardipine hydrochloride tablet before and after irradiation for 14 d under the white fluorescent lamp. The absorption peak at 1700 cm^{-1} attributable to the

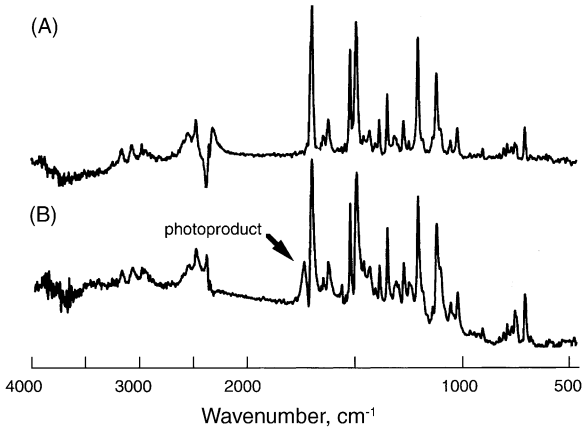

Fig. 5. Changes in FT-IR-RAS spectra of β-form of nicardipine hydrochloride before and after irradiation: (A) before irradiation; (B) after 14-d irradiation.

C=O stretch vibration of β-form decreased after irradiation and a new band appeared at 1734 cm^{-1}. The C=O stretch vibration band of pyridine derivative of nifedipine photoproducts was shifted to slightly higher wavenumber (Teraoka et al., 1999). In addition, the results obtained by a photodiode array detector showed that a pyridine derivative of nicardipine hydrochloride formed by light irradiation. The photodegradation of nicardipine hydrochloride solutions was investigated (Bonferoni, 1992) and the pyridine analog yielded after exposure to UV and daylight. This suggested that the residual nicardipine hydrochloride on the tablet surface decreased by photodegradation and a nitro-derivative formed.

The calibration curve for carbamazepine on the surface of pellet established good linearity and the reproducibility of the data was good (Matsuda et al., 1994). FT-IR-RAS method also allowed the separation of the intact nicardipine hydrochloride from the photoproducts in this study. Therefore, we used the absorbance of the C=O stretch band to measure the residual amount of the drug and the absorbance ratio of the C=O group at 1700 cm^{-1} before and after irradiation was calculated as the apparent residual nicardipine hydrochloride.

Fig. 6 shows the time-courses of the photodegradation of nicardipine hydrochloride tablets prepared with the two crystal forms and the ground samples under the irradiation by fluorescent lamp. The residual amount of the β-form ground decreased to approximately 10% after 12-d irradiation. On the other hand, about 40%

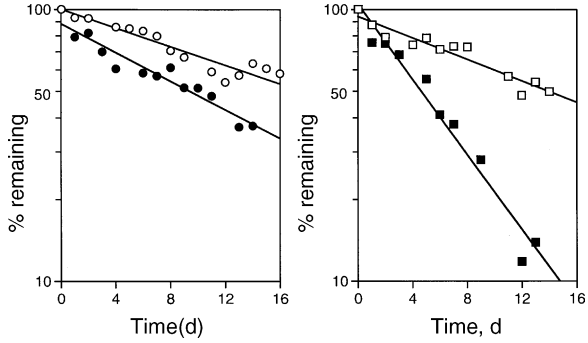

Fig. 6. Effect of grinding on the solid-state photostability of α- and β-forms of nicardipine hydrochloride (◯,●): α-form; (□,■): β-form. The open and closed symbols represent the intact and ground powder after 150 min, respectively.

of intact amount remained in the case of the α-form ground after the same irradiation time. These results indicated that there was the significant difference in photostability between the ground sample of α-form and that of β-form.

Straight lines were obtained on the semilogarithmic scale for all tablets, indicating that photodegradation of the drug on the tablet surface followed apparently the first-order kinetics. Thus the degradation rate constants for these tablets were estimated from the linear part of the lines by least-squares method.

Table 1 summerizes photodegradation rate constants and the values of $\triangle E$ after 7-d irradiation for α- and β-forms. The values of $\triangle E$ of β-form and the ground sample exhibited approximately the same values, whereas the photodegradation rate constant for the β-ground sample was 3.5 times greater than that for β-form. Consequently, the appearance change was not in agreement with the degradation amount. This result suggested that it was difficult to estimate chemical stabil-

Table 1
Effect of grinding on the photodegradation rate constant and color difference ($\triangle E$) after 7-d irradiation

	Degradation rate constant (d^{-1})	Color difference ($\triangle E$) after 7-d irradiation
α-Form		
Intact	0.039	3.5
Ground for 150 min	0.061	6.5
β-Form		
Intact	0.046	13.1
Ground for 150 min	0.159	12.9

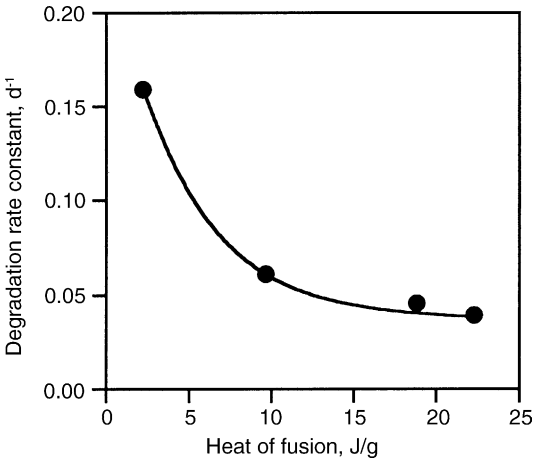

Fig. 7. Relationship between heat of fusion and photodegradation rate constant.

ity of nicardipine hydrochloride from the appearance change.

The photodegradation rate constants for β-form of lower melting point became greater than that for α-form. It has become apparent that β-form was less stable to light. The relation between the crystal structure of titanylphthalocyanine and its absorption spectrum in the solid state was investigated in detail (Mizuguchi et al., 1995). It was evident that the absorption spectrum in the solid state depends largely on the crystal form. Therefore, it would be thought that the two forms of nicardipine hydrochloride have its own absorption spectrum and the difference in photoreactivity was observed consequently among these crystal forms.

Both of the ground samples of two crystal forms decomposed much faster than each intact crystal and the ground sample of β-form was much more subject to photodegradation. It is considered that the ground sample had poor stability because the degree of crystallinity decreased by mechanochemical effect and due to the increase of internal energy. Fig. 7 illustrates the relationship between the photodegradation rate constant and heat of fusion measured by DSC profiles. The degradation rate constant decreased with increasing the heat of fusion. This suggested that the light stability depended on the crystal form and that the drug of the lower crystallinity was unstable both thermodynamically and photochemically.

4. Conclusion

It was proved that nicardipine hydrochloride in the solid state decomposed to a pyridine analog after oxidation of dihydropyridine ring by the light irradiation. Photodegradation of the ground crystals of the two forms was accelerated and this effect of grinding was especially significant for β-form crystals. The photostability of those powders decreased with the increase of internal energy of crystal.

FT-IR-RAS method is a simple and useful method for quantification of topochemical reaction such as solid-state photodegradation.

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