ELSEVIER

International Journal of Pharmaceutics 184 (1999) 35–43

international journal of pharmaceutics

Evaluation of photostability of solid-state dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitro-phenyl)-3, 5-pyridinedicarboxylate by using Fourier-transformed reflection-absorption infrared spectroscopy

Reiko Teraoka *, Makoto Otsuka, Yoshihisa Matsuda

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

Received 5 November 1998; received in revised form 20 January 1999; accepted 17 February 1999

Abstract

Effect of particle size on the photostability of dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitro-phenyl)-3,5-pyridinedicarboxylate (nifedipine) powder and its tablet was investigated using high-pressure liquid chromatography (HPLC) method and Fourier-transformed infrared reflection-absorption spectroscopy (FT-IR-RAS) under the non-destructive condition. The nifedipine content on the surface of the tablet was determined based on the absorbance at 1682 cm^{-1} attributable to the C=O stretch vibration in FT-IR-RAS spectra before and after irradiation by fluorescent lamp. The photodegradation followed apparently the first-order kinetics for any sample. The apparent photodegradation rate constant of nifedipine powder increased with decrease of the particle size, while that of its tablet was approximately constant irrespective of particle size. Semilogarithmic plots of the apparent degradation rate constant for nifedipine tablet against the reciprocal of illuminance demonstrated a linear relationship similar to that of the Arrhenius-type behavior.

Keywords: Nifedipine; Photostability; Fourier-transformed reflection-absorption infrared spectroscopy; Photostability test; Preformulation; Solid state

1. Introduction

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (nifedipine) is an effective calcium antagonist and has been widely used for the treatment of coronary heart disease. Because of its instability to light, the drug should be stored carefully.

Preformulation study of new drug is important in development process of drug and in quality assurance after manufacture. Chemical and physical stability testings of pharmaceutical substances are investigated under various temperature, humidity and light conditions. There are many reports concerning photostability of organic

* Corresponding author.

0378-5173/99/$ - see front matter
PII: S0378-5173(99)00089-7

compounds in solution (Matsumoto et al., 1981; Akimoto et al., 1989; Tammilehto and Tornianen, 1989; Matsuura et al., 1990; Teraoka and Matsuda, 1993). However, there are fewer reports concerning the photostability of solid dosage forms (Akimoto et al., 1985; Matsuda et al., 1989) because stability data are not fully reproducible due to the ununiformity of reaction in the solid state.

Fourier-transformed infrared reflection-absorption spectroscopy (FT-IR-RAS) allows pure materials to be analyzed without addition of KBr (Golden, 1985). Although the appearance change of solid pharmaceutics is important from the point of view of the qualitative evaluation, colorimetric measurement relates only to physicochemical properties and does not offer any chemical information. On the other hand, the FT-IR-RAS can offer chemical information as well as physicochemical properties. Recently, photostability of carbamazepine polymorphs was investigated by using FT-IR-RAS (Matsuda et al., 1994). The photodegradation of pharmaceuticals is a topochemical reaction, therefore, it is not appropriate to evaluate the decomposition ratio by conventional analytical methods such as high-pressure liquid chromatography (HPLC), ultraviolet (UV), and infrared (IR) spectroscopy. Therefore, FT-IR-RAS is used to measure pure materials using its tablets.

In this study, a simple and fast FT-IR-RAS method is described for quantitative determination of nifedipine in order to improve the reproducibility of the data on the photostability test, and then the results were compared with the data obtained from the photostability test using powder samples.

2. Materials and methods

2.1. Materials

Bulk nifedipine powder was obtained from Kanebo, Japan, and was sieved. The average

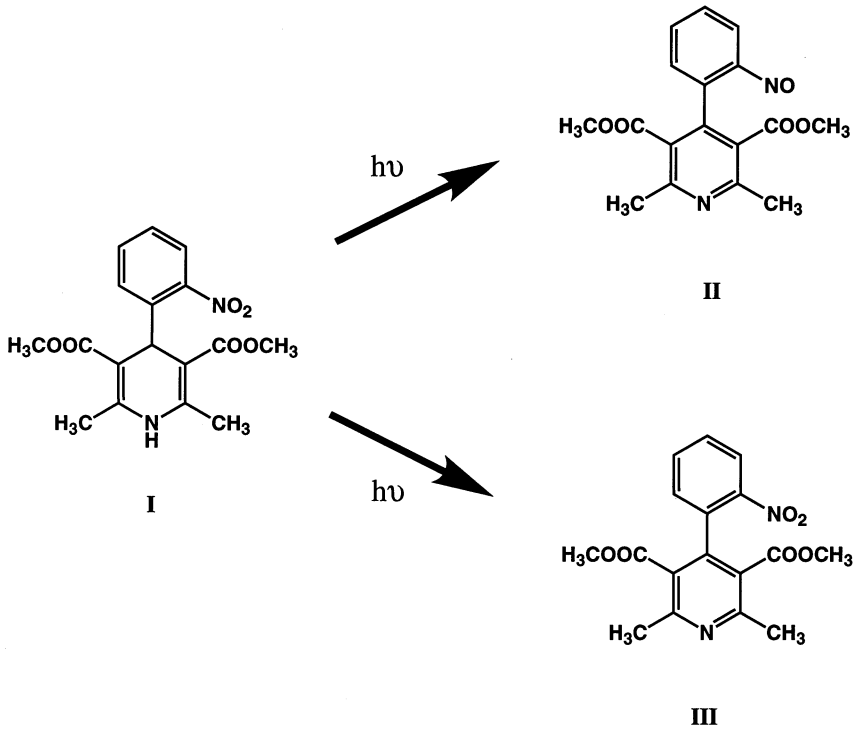

Fig. 1. Nifedipine and its main photodegradation products.

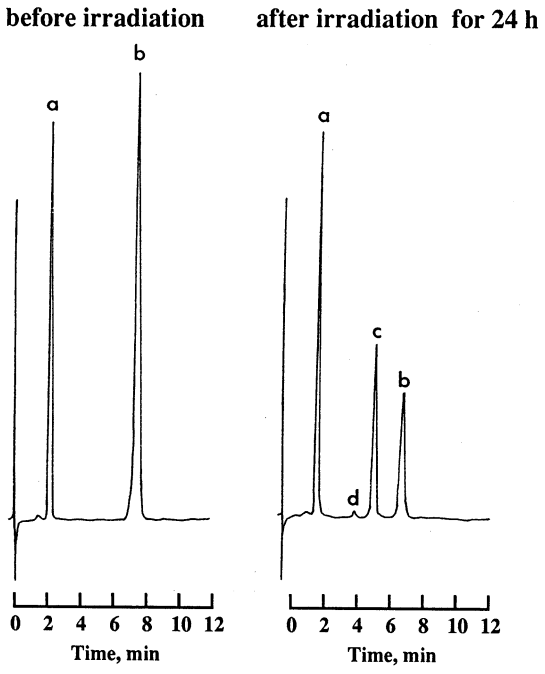

Fig. 2. High-pressure liquid chromatography (HPLC) chromatograms of nifedipine and its photoproducts. (a) Ethyl *p*-aminobenzoate(internal standard); (b) nifedipine; (c) nitroso-derivative; (d) nitro-derivative.

value of the upper and lower sieve openings was used as the mean particle size and five types of the powders were prepared in the range of 127–324μm. The commercial solvents for HPLC analysis and *p*-aminobenzoic acid ethyl ester were used without further purification.

2.2. Preparation of sample pellets

The sieved nifedipine powder (500 mg) were compressed using an accurate compression/tension testing machine (Autograph model IS-5000, Shimadzu, Kyoto, Japan) equipped with flat-faced punches and a cylindrical die (20 mm i.d.) set at a compression speed of 15 mm min^{-1} at 1000 kg cm^{-2}.

2.3. Irradiation test

Sample pellet or sieved powder (5 mg) were stored in a light-irradiation tester (LIGHTTRON LT-120, Nagano Science Equipment MFG, Takatsuki, Japan) equipped with source is 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.

2.4. X-ray powder diffraction analysis

Diffractograms were taken at room temperature with an X-ray diffractometer (XD-3A, Shimadzu, Kyoto, Japan). 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 2θ 4° min^{-1}. The X-ray diffraction profiles of the five powders were not significantly different in diffraction patterns, indicating that all kinds of the powders had the same crystalline structure.

2.5. FT-IR measurement

The sample powder was dispersed in KBr powder (sample concentration 5%) and analyzed. FT-IR spectra were obtained by powder-diffused reflectance on an FT-IR spectrophotometer (model FT-IR 1600, Perkin Elmer, Yokohama, Japan) and corrected using the Kubelka–Munk equation.

2.6. FT-IR-RAS measurement

FT-IR spectra of the sample pellets were obtained by FT-IR-RAS on an FT-IR spectrometer and modified by using the Kramer–Krönig equation.

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, Tokyo, Japan) after the designated irradiation times. The color difference (ΔE) (Matsuda et al., 1989) before and after irradiation was calculated to evaluate the degree of discoloration. All values were the averages of two measurements.

2.8. HPLC analysis

The HPLC system consisted of Waters LC pump (model 510) and autosampler (Waters, model 717), a 15 cm × 4.6 mm YMC-Pack ODS-AQ (5 μm) column (YMC, Japan), an UV detector (model SPD-2A; Shimadzu, Kyoto, Japan) with the detection wavelength of 234 nm and a Maxima 820 Chromatography Workstation (Waters, USA). The mobile phase consisted of methanol–water (55:45) with flow rate of 1.3 ml min^{-1}. *p*-Aminobenzoic acid ethyl ester solution (2.5 g/l) was used as an internal standard. After irradiation, sample powder was dissolved in 5 ml of the internal standard solution. Prior to injection into HPLC columns, 0.5 ml of the solution was diluted with 5 ml of methanol, and the remaining nifedipine was calculated from the nifedipine/internal standard peak height ratio.

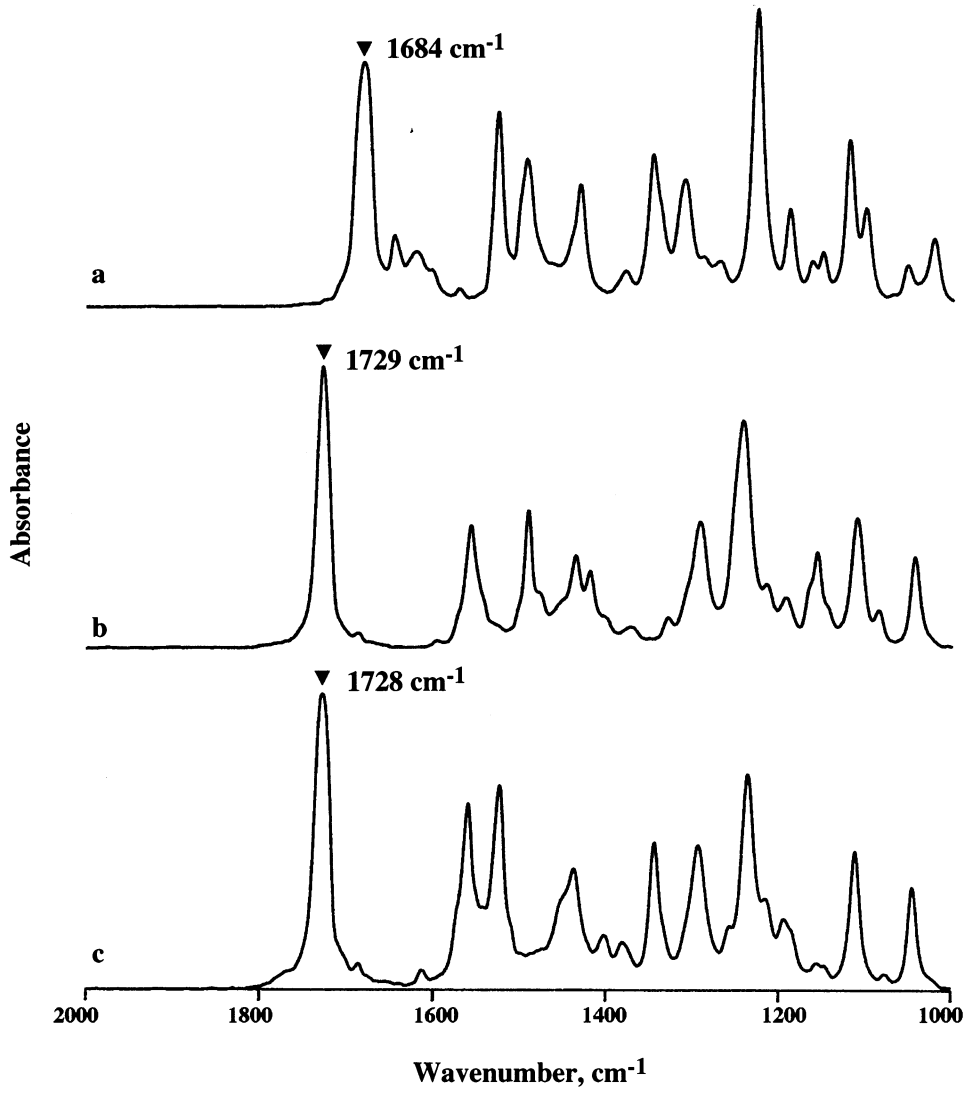

Fig. 3. The diffuse reflectance Fourier-transformed infrared (FT-IR) spectra of nifedipine and its photoproducts. (a) Nifedipine; (b) nitroso-derivative; (c) nitro-derivative

3. Results and discussion

3.1. Photodegradation of nifedipine powder investigated by HPLC

There have been many reports on the photodegradation of nifedipine under the UV or visible light (Kudo et al., 1972; Ebel et al., 1978; Jakobsen et al., 1979; Binda and Dondi, 1981; Terui et al., 1984; Inoue et al., 1985; Majeed et al., 1987; Sadana and Ghogare, 1991).

Matsuda et al. (1989) reported that irradiation of the solid-state nifedipine using a mercury vapor lamp or fluorescent lamp mainly produced 4-(2-nitrosophenyl) - 2,6 - dimethyl - 3,5 - dimethoxycar - bonyl-pyridine (nitroso-derivative) (II) and 4-(nitrophenyl) - 2,6 - dimethyl - 3,5 - dimethoxycarbonyl - pyridine corresponding to the dehydrogenated form (nitro-derivative) (III) (Fig. 1).

Fig. 2 shows typical chromatograms of the sieved nifedipine powder irradiated by a white fluorescent lamp for 24 h. It exhibited that two peaks were attributable to photoproducts other than (b) of the intact nifedipine. The retention times for products (c) and (ed) agreed exactly with those for the authentic samples of the nitroso-derivative and nitro-derivative, respectively. The nitroso-derivative was formed predominantly under the irradiation of fluorescent lamp.

3.2. Evaluation of photodegradation on the surface of nifedipine tablets

Fig. 3 shows the FT-IR spectra of nifedipine, the nitroso-derivative (II) and nitro-derivative (III) obtained by FT-IR diffuse-reflectance method. The bands attributable to the carbonyl group of nifedipine, the nitroso-derivative, and nitro-derivative were 1684, 1729, and 1728 cm^{-1}, respectively. The strong absorption band due to the C=O stretching mode could be distinguished clearly between the intact nifedipine and the two photoproducts.

Fig. 4 shows the FT-IR-RAS spectra of nifedipine tablet before and after irradiation for 40 min under the fluorescent lamp. The absorption peak at 1682 cm^{-1} attributable to the C=O stretch vibration of (I) decreased significantly after irradiation and a new band at 1731 cm^{-1} appeared. This suggested that the residual nifedipine on the tablet surface decreased by photodegradation and the nitroso-derivative (II) or nitro-derivative (III) formed.

Matsuda et al. (1994) have reported that the calibration curve for carbamazepine on the surface of pellet established good linearity and that the reproducibility of the data was good.

FT-IR-RAS method also allowed the separation of the intact nifedipine from photoproducts. Therefore, the absorbance of the C=O stretch band was used to measure the residual amount of nifedipine and the absorbance ratio of C=O group at 1682 cm^{-1} before and after irradiation was calculated as the residual nifedipine.

3.3. Effect of particle size on the photostability of nifedipine powder and tablet

Fig. 5(a) shows the time-courses of the photodegradation of nifedipine powder with various particle sizes under the irradiation by fluorescent lamp. The degradation of nifedipine powder was found to follow apparently the first order kinetics. The percent remaining after 24 h-exposure for the127- and 324-μm samples were 16.0 and 44.3, respectively. These results indicate a rapid increase in percent remaining occurred with increasing particle size. Fig. 5(b) shows the time-courses of the photodegradation of nifedipine tablet prepared with the same powder in Fig. 5(a) under the irradiation by a fluorescent lamp. Straight lines were also obtained on the semilogarithmic scale for all tablets, indicating that photodegradation of the drug on the tablet surface followed apparently the first-order kinetics. The degradation rate constants for each powder and tablet were estimated from the linear part of the lines by the least-squares method.

The effect of particle size on the photodegradation rate constant of nifedipine powder and its tablet is illustrated in Fig. 6. The photodegradation rate constant for nifedipine powder depended on the particle size and decreased with an increase in the particle size.

De Villers et al. (1993) reported on the effect of cohesiveness of small particles on the solid-state

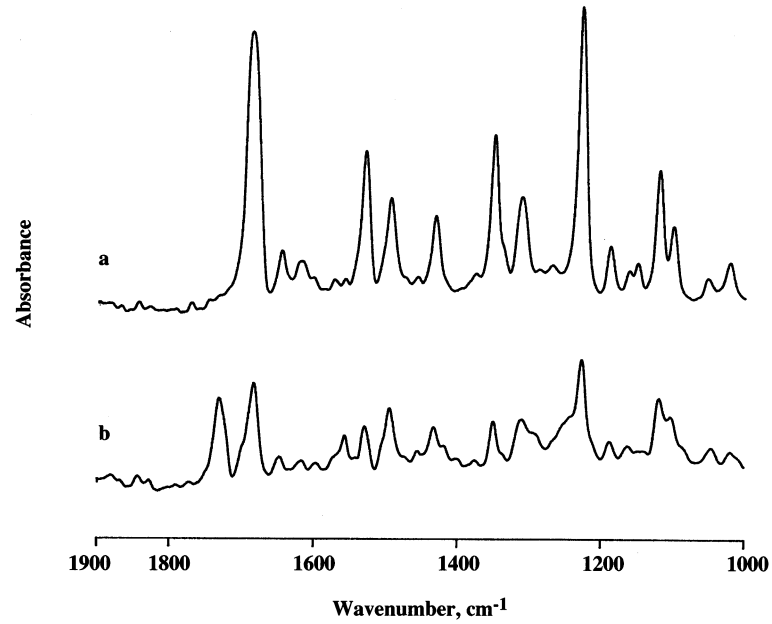

Fig. 4. Changes in Fourier-transformed infrared reflection-absorption spectroscopy (FT-IR-RAS) spectra of nifedipine before and after irradiation. (a) Before irradiation; (b) after irradiation.

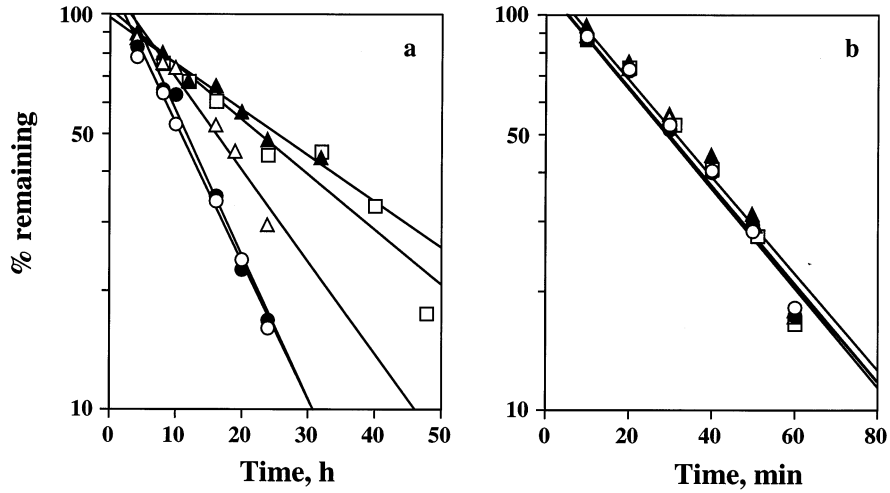

Fig. 5. Effect of particle size on the photostability of nifedipine powder and its tablet. (a) Powder; (b) tablet. Particle size: ○, 127 μm; ●, 180 μm; △, 230 μm; ▲, 274 μm; □, 324 μm.

photochemical degradation of furosemide. They stored agglomerated furosemide and its dispersed particles after recrystallization (separate lot) under the irradiation by direct sunlight for up to 240 h. The separated particles degraded more rapidly than the agglomerated particles. Although the real mean particle size of primary particles (2.5 μm) of the agglomerates was significantly smaller than that of the dispersed particles (22 μm), the mean particle sizes of the agglomerates (200–250 μm) were inversely by far larger than that of the dispersed particles.

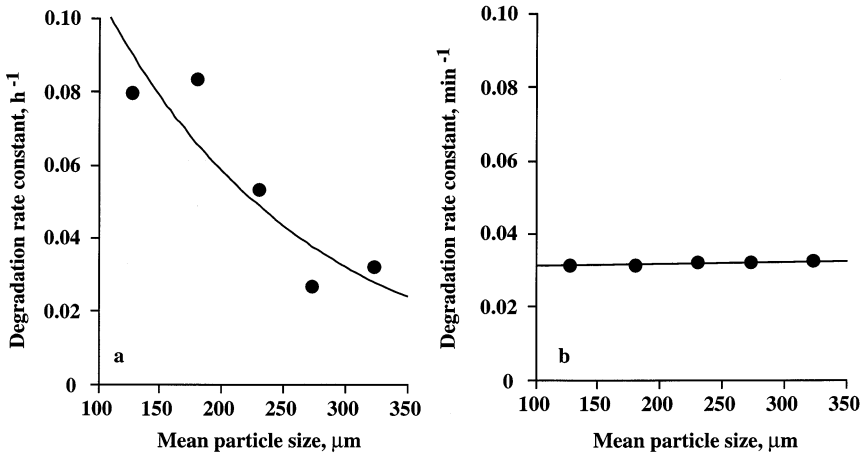

Fig. 6. Effect of particle size on the photodegradation rate constant of nifedipine powder and its tablet. (a) Powder; (b) tablet. Particle size: ○, 127 μm; ●, 180 μm; △, 230 μm; ▲, 274 μm; □, 324 μm.

It seemed that the amount of degradation in powder depended on the surface area exposed to sun light.

On the other hand, the photodegradation rate constants for nifedipine tablets were almost constant irrespective of the particle size. The photodegradation rate constant in the solid state varies widely by various factors such as crystal form, particle size, and irradiation area. Therefore, the data for the stability test was qualitative and it is difficult to compare degradation rate constants quantitatively. The FT-IR-RAS method using the tablet was superior to the HPLC method using drug powder because the particle size had apparently no effect on the photodegradation. The results suggested that FT-IR-RAS would be an excellent estimation method for photostability test.

3.4. Effect of particle size on the appearance change of nifedipine tablet

As has already been reported on the kinetics of discoloration of the nifedipine tablet (Matsuda et al., 1989), it is possible to calculate the apparent order of reaction (n) and discoloration rate constant (k) using Eqs. (1) and (2).

$$\frac{d\Delta E}{dt} = k(\Delta E)^n \quad (1)$$

$$\log \Delta E = \frac{1}{1-n} \log t + \frac{1}{1-n} \log[(1-n)k] \quad (2)$$

where ΔE, t and k are color difference, irradiation time and the color darkening rate constant, respectively, and n is constant.

Fig. 7 shows the double-logarithmic plots of color darkening processes of tablet prepared with various particle sizes under the irradiation by the fluorescent lamp. The plots gave excellent straight lines over the whole range of irradiation time

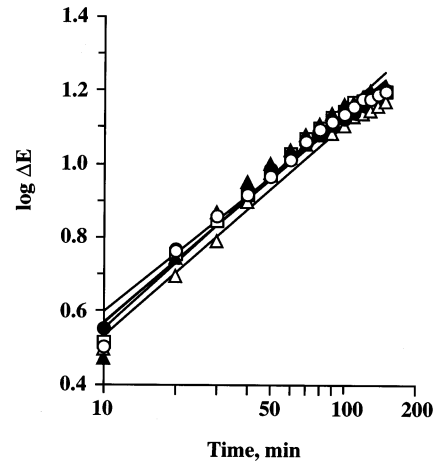

Fig. 7. The double-logarithmic plots for the color change process of nifedipine tablet prepared with powder of various particle sizes under fluorescent lamp. Particle size: ○, 127 μm; ●, 180 μm; △, 230 μm; ▲, 274 μm; □, 324 μm.

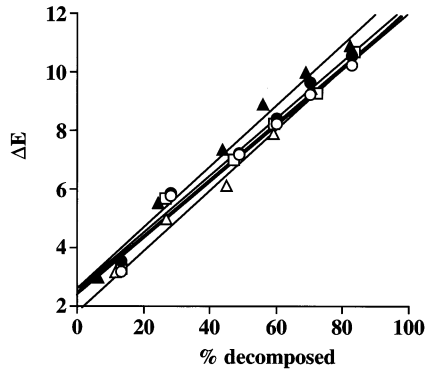

Fig. 8. Relationship between color difference (ΔE) and percent decomposed. Particle size: ○, 127 μm; ●, 180 μm; △, 230 μm; ▲, 274 μm; □, 324 μm.

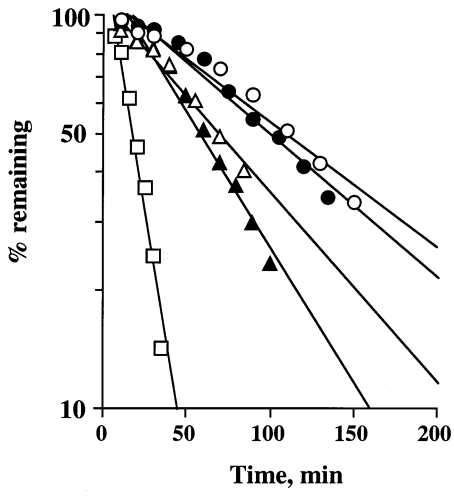

Fig. 9. Effect of illuminance on the photodegradation of nifedipine tablet. Illuminance (lx): ○, 1300; ●, 1600; △, 2000; ▲, 2500; □, 7500.

investigated and the slopes calculated from the regression lines was almost the same. This result was similar to that obtained in Fig. 5, indicating that the difference in color change is dependent on the chemical degradation.

Fig. 8 shows the relation between ΔE and decomposition of nifedipine tablets. Good correlations were observed between the apparent percent decomposed and ΔE for all tablets, and the slopes calculated from regression lines were almost the same. The results suggested that the surface decomposition could be estimated by using the ΔE value obtained by colorimetric measurement.

3.5. Effect of illuminance on the photodegradation of nifedipine tablets

The effect of illuminance on the photostability of nifedipine tablets was studied. Fig. 9 shows semilogarithmic plots of the percent remaining of nifedipine measured by the FT-IR-RAS method against time at different illuminances under the irradiation by the fluorescent lamp. The plots showed good linearity over the wide rage of illuminances investigated. Nifedipine on the surface of the tablet degraded rapidly with increasing illuminance. Thus the effect of illuminance on the degradation rate constant is illustrated in Fig. 10. Semilogarithmic plots of the apparent degradation rate constant against the reciprocal of illuminance conformed closely to a linear relationship, as well as the results obtained by Teraoka and Matsuda (1993), Mendenhall (1984) and Tokunaga et al. (1985) similar to that of the Arrhenius-type behavior. This result suggests that the photostability under an ordinary illumination condition can readily be predicted from the data obtained under the accelerated condition of illumination. T_{90} (time required for 10% degradation) calculated from the regression line was 22 h at 500 lx which is recommended as the standard illuminance in hospital pharmacy. The results indicate

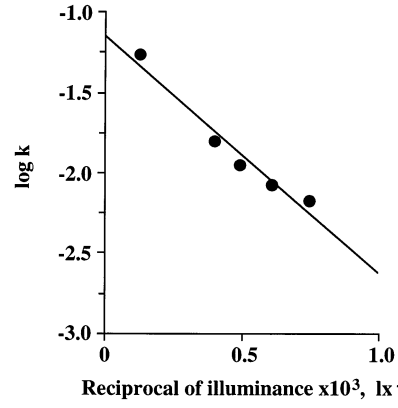

Fig. 10. Semilogarithmic plots of apparent degradation rate constant against the reciprocal of illuminance.

that nifedipine is unstable extremely and care must be taken in hand.

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

References

Akimoto, K., Inoue, K., Sugimoto, I., 1985. Photostability of several crystal forms of cianidanol. Chem. Pharm. Bull. 33, 4050–4053.

Akimoto, K., Matsumoto, J., Nakagawa, H., Sugimoto, I., 1989. Photo-stability of 1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl) piperazine dihydrochloride (KB-2796) and its analogs in aqueous solution. Yakuzaigaku 49, 9–15.

Binda, M.L., Dondi, G., 1981. Studio sull'influenza della e dei coloranti sulla stabilita di nifedipina capsule. Boll. Chim. Farm. 120, 544–551.

De Villers, M.M., van der Watt, J.G., Lötter, A.P., 1993. Influence of the cohesive behavior of small particles on the solid-state photolytic degradation of furosemide. Drug. Dev. Ind. Pharm. 19, 383–394.

Ebel, V.S., Schutz, H., Hornitschek, A., 1978. Untersuchungen zur Analytik von Nifedipin under besonderer Berücksichtigung der bei Lichtexposition entstehenden Umwandlungsprodukte. Arzneim.-Forsch. 28, 2188–2193.

Golden, W.G., 1985. In: Ferraro, J.R., Basile, L.J. (Eds.), Fourier Transform Infrared Spectroscopy. Academic Press, New York, p. 315.

Inoue, K, Washiyama, A., Kimura, K., Kuroda, T., 1985. Stability of commercial nifedipine preparations. Byoin Yakugaku 11, 267–275.

Jakobsen, P., Pedersen, O.L., Mikkelsen, E., 1979. Gas chromatographic determination of nifedipine and one of its metabolites using electron capture detection. J. Chromatogr. 162, 81–87.

Kudo, A., Sakai, J., Yukino, H., Sueshige, F., Kamiyama, K, 1972. The stability of substance Bay 1040 and its preparations. Kiso to Rinsho 6, 259–276.

Majeed, I.A., Murray, W.J., Newton, D.W., Othman, S., Alturk, W.A., 1987. Spectrophotometric study of the photodecomposition kinetics of nifedipine. J. Pharm. Pharmacol. 39, 1044–1046.

Matsuda, Y., Teraoka, R., Sugimoto, I., 1989. Comparative evaluation of photostability of solid-state nifedipine under ordinary and intensive light irradiation conditions. Int. J. Pharm. 54, 211–221.

Matsuda, Y., Akazawa, R., Teraoka, R., Otsuka, M., 1994. Pharmaceutical evaluation of carbamazepine modifications: comparative study for photostability of carbamazepine polymorphs by using Fourier-transformed reflection-absorption infrared spectroscopy and colorimetric measurement. J. Pharm. Pharmacol. 46, 162–167.

Matsuura, I., Imaizumi, M., Sugiyama, M., 1990. Method of kinetics analysis of photodegradation: nifedipine in solutions. Chem. Pharm. Bull. 38, 1692–1696.

Matsumoto, H., Isobe, A., Ohnishi, Y., 1981. Effects of various environmental factors on the photodecomposition of 2,4,4′-trichloro-2′-hydroxydiphenylether (Irgasan DP300) in alkaline solution. Yakuzaigaku 41, 88–93.

Mendenhall, D.W., 1984. Stability of parenterals. Drug Dev. Ind. Pharm. 10, 1297–1342.

Sadana, G.S., Ghogare, A.B., 1991. Quantitative proton magnetic resonance spectroscopic determination of nifedipine and its photodecomposition products from pharmaceutical preparations. J. Pharm. Sci. 80, 895–898.

Tammilehto, A., Tornianen, K., 1989. Photochemical stability of dothiepin in aqueous solutions. Int. J. Pharm. 52, 123–128.

Teraoka, R., Matsuda, Y., 1993. Stabilization-oriented preformulation study of photolabile menatetrenone (vitamin K_2). Int. J. Pharm. 93, 85–90.

Terui, K., Shinoyama, R., Sone, K., Fujita, K., 1984. Influence of light on the quality of commercial nifedipine preparations. Byoin Yakugaku 10, 224–228.

Tokunaga, H., Kimura, T., Kawamura, J., Yamaha, T., 1985. Stability of ergometrine maleate in aqueous solution. Iyakuhin Kenkyu 16, 130–135.