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Pharmaceutical Evaluation of Carbamazepine Modifications: Comparative Study for Photostability of Carbamazepine Polymorphs by using Fourier-transformed Reflection-absorption Infrared Spectroscopy and Colorimetric Measurement

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Abstract—The tablet surface was evaluated without physical damage by means of Fourier-transform infrared reflection-absorption spectroscopy (FT-IR-RAS) and colorimetric measurement (colour difference, ΔE) of the carbamazepine polymorphs I, II and III, after photodegradation at two irradiation intensities (3·0 and 12·0 J cm^{-2} s^{-1}) under a near-UV fluorescent lamp. The surface of sample pellets of all crystalline forms turned gradually from white to yellow-orange upon exposure to light, and the discoloration rate of form II was faster than that of forms I and III, indicating that form II was the most unstable of the three. The major photoproducts were identified by HPLC, NMR and MS analyses. The carbamazepine content on the surface of the tablet was determined based on the absorption at 1685 cm^{-1} atributable to C=O stretch vibration in the FT-IR-RAS spectra before and after irradiation by a near-UV fluorescent lamp. The semilogarithmic plots of the photodegradation profiles of the various polymorphs were straight lines, including the induction period, indicating that degradation of the drug on the surface followed first-order kinetics. The induction periods of all forms were not significantly different. However, the degradation rate constant of form II at 12.0 J cm^{-2} s^{-1} was 5·1 and 1·5 times larger than those of forms I and III, respectively.

Preformulation studies are of prime importance in the rational development of dosage forms of labile drugs. To design a dosage form, it is necessary to know the inherent stability of the drug against stimuli, such as heat, humidity and light. There are many reports concerning the solid-state stability of organic compounds under various conditions of temperature and humidity (Carstensen 1990; Yoshioka 1990). Photolabile drugs have been adequately protected from photolytic degradation by packaging in light-resistant systems (Teraoka et al 1989); however, there are fewer reports concerning the photostability of solid dosage forms (Matsuda & Teraoka 1985).

The presence of polymorphs and amorphous forms of drugs affect the solid-state stability of the preparations against various environmental factors (Otsuka & Kaneniwa 1991). Thus, the pharmaceutical design of drugs, especially those of polymorphic forms, is important for high quality pharmaceuticals. Carbamazepine is widely used as a potent anticonvulsant, and there have been many reports concerning its polymorphic modifications (Pöhlmann et al 1975), hygroscopicity (Kaneniwa et al 1984), dissolution rates (Kaneniwa et al 1987), crystalline transformation at high temperature conditions (Umeda et al 1984; Behme & Brooke 1991) and behaviour under aqueous conditions (Laine et al 1984; Young & Suryanarayanan 1991). The dissolution rate and bioavailability (Kahela et al 1983) of carbamazepine in man, its physicochemical stability under grinding and compression (Lefebvre et al 1986), and the chemical stability (Krahn & Mielck 1989) of polymorphic forms at high humidity have also been investigated during formulation studies. Since carbamazepine is degraded and transformed by sun-lamp irradiation into the highly toxic 10, 11-epoxide, its photostability was investigated as part of a formulation study (Baker et al 1973).

Recently, samples have been investigated at the molecular level by Fourier-transform infrared (FT-IR) spectroscopy. Hartauer et al (1992) used powder-diffuse reflectance infrared Fourier-transform spectroscopy to estimate the polymorphic forms of the drug, and quantified a mixture of polymorphs. However, since they used the mixture of drug and KBr powders, it was difficult to measure the pure compound. However, Fourier-transform infrared reflection-absorption spectroscopy (FT-IR-RAS) (Golden 1985) allows pure materials to be analysed without addition of KBr.

The photodegradation of pharmaceuticals in tablet form is a topochemical reaction, therefore, it is not appropriate to evaluate the decomposition ratio by conventional analytical methods such as HPLC, UV and IR spectroscopy. Therefore, we used FT-IR-RAS to measure pure materials on the surface of tablets.

Materials and Methods

Materials

Bulk carbamazepine powder of JP grade (lot No. CEC-5-1) was obtained from Katsura Chem. Co., Tokyo, Japan. Microcrystalline cellulose was Avicell PH-101 (Lot. 1983, Asahikasei Co., Ltd). Standard carbamazepine cyclo butyl dimer was prepared as previously described (Robson & Sharples 1984). Standard carbamazepine 10,11-epoxide was

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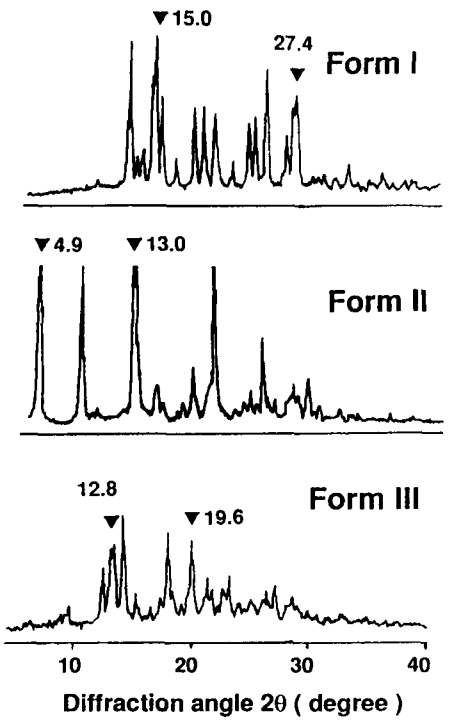

FIG. 1. Powder X-ray diffraction profiles of three carbamazepine polymorphs.

obtained from Ciba-Geigy Japan Ltd, Takarazuka, Japan. All other chemicals were of analytical grade.

Preparation of polymorphs

Three modifications of the drug were prepared by various means as previously described (Kaneniwa et al 1984), form I (anhydride) was the bulk powder. Form II (anhydride) was precipitated from a saturated chloroform solution of the drug by pouring in ethyl ether, and stirring for 1 h at room temperature (21°C), the separated crystals were then filtered and dried in-vacuo in a desiccator containing P_2O_5 at room temperature for 3 h. Form III (anhydride) was obtained by heating form IV at 115°C in-vacuo for 6 h. The sample powders were passed through a No. 145 mesh screen (105 μm) and did not pass through No. 300 mesh (46 μm).

Preparation of sample pellets

The sample powders (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^{-1} at 1000 kg cm^{-2}.

X-ray powder diffraction analysis

Diffractograms were taken at room temperature with an X-ray diffractometer (XD-3A, Shimadzu Co., Kyoto, Japan). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 25 kV; current, 10 mA; receiving slit, 0·1 mm; time constant, 1 s; counting range, 1000 counts s^{-1}; scanning speed 4° 2θ min^{-1}.

Irradiation test

Sample pellets were stored in a tight plastic container with a quartz glass window containing a $MgCl_2$. $6H_2O$ saturated solution (31% relative humidity (r.h.)) at 45·0±0·1°C, and irradiated in a light-irradiation tester (LT-120, Nagano Sci. Co., Osaka, Japan) with a near-UV fluorescent lamp.

Mass spectrometry (MS)

MS spectra were obtained with an M-80 type mass spectrometer (Hitachi Co., Japan).

Nuclear magnetic resonance (NMR) spectroscopy

CF_3COOD solvent contained about 3% sample. The proton NMR spectra were recorded at 500 MHz (model XL-500; Varian).

Thermal analysis

Differential scanning calorimetry (DSC) was performed with a type 3100 instrument (Mac Science Co., Tokyo, Japan). The operating conditions in the open-pan system were as follows: sample weight, 5 mg; heating rate, 10°C min^{-1}; N_2 gas flow rate, 50 mL min^{-1}.

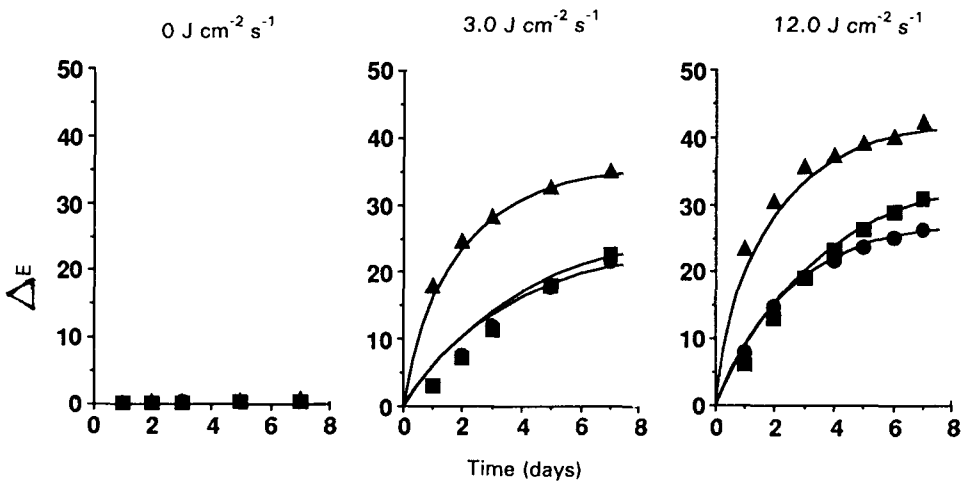

FIG. 2. Time courses for discoloration of polymorphs at various intensities under near-UV fluorescent light. ● I, ▲ II, ■ III.

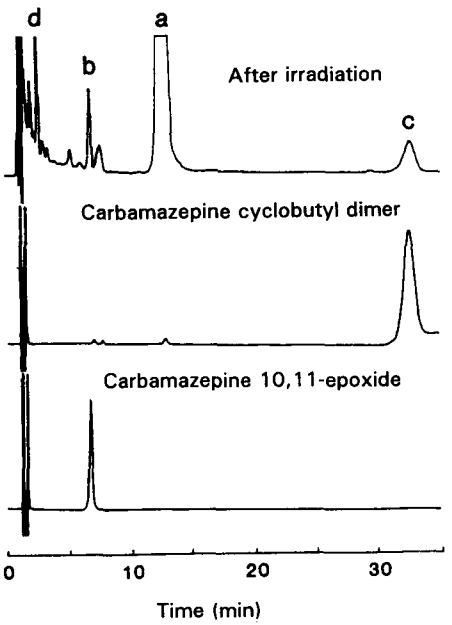

FIG. 3. HPLC of carbamazepine and its photoproducts. a. Carbamazepine, b. carbamazepine 10, 11-epoxide; c. carbamazepine cyclobutyl dimer, d. unknown products.

FT-IR measurement

The sample powder was dispersed in KBr powder (sample concentration 5%) and analysed. FT-IR spectra were obtained by powder-diffuse reflectance on an FT-infrared spectrophotometer (type FT-IR 1600, Perkin Elmer Co., Yokahama, Japan) and corrected using the Kubelka-Munk equation.

FT-IR-RAS measurement

FT-IR spectra of the sample pellets were obtained by FT-IR-RAS on an FT-infrared spectrophotometer (type FT-IR 1600, Perkin Elmer Co., Yokohama, Japan) and modified using the Kramers-Krönig equation. Various concentrations of standard carbamazepine for quantitative analysis were prepared by physically mixing forms I, II or III and crystalline cellulose. Each value was an average of five measurements.

Colorimetric measurement

The surface colour of the compressed sample pellet was measured with an integrating sphere-type colour difference meter (model ND-300A, Nippon Denshoku Co., Tokyo, Japan) after irradiating for various periods. The colour difference (ΔE) (Matsuda et al 1989) before and after irradiation was calculated to evaluate the degree of discoloration. All values were averages of two measurements.

High-pressure liquid chromatography (HPLC) analysis

Carbamazepine was analysed with an HPLC system consisting of a solvent delivery system (LC-5A, Shimadzu Co., Kyoto, Japan), and photodiode array detector (model 991J, Waters Associates) operated at 190–400 nm. The prepacked column (μBondasphere 5 μm Phenyl-100 Å; 3·9 mm i.d. × 15 cm, Waters Associates) was operated at room temperature at a flow rate of 1·2 mL min^{-1}. The mobile phase consisted of acetonitrile: 0·05 M ammonium acetate buffer (20:80). After the storage experiments, about 7·5 μm of the pellet surface was removed with a razor, and diluted with methanol. The sample and standard solutions were injected into the chromatograph to identify the decomposition products of carbamazepine.

Results and Discussion

Physicochemical properties of modified carbamazepine

Fig. 1 shows the X-ray powder diffraction profiles of forms I, II and III. The diffraction patterns and the DSC curves of all crystalline forms were significantly different and identical to reported data (Pöhlmann et al 1975; Kaneniwa et al 1984, 1987). The stability of crystalline carbamazepine forms after mechanical stress by compression at 1000 kg cm^{-2} was checked by carefully grinding pellets with an agate mortar and pestle, then taking the X-ray powder diffraction profiles. The X-ray diffraction profiles of all compressed crystal forms were identical to those of the original samples. The X-ray diffraction patterns suggested that no crystallographic changes had occurred during compression under our experimental conditions.

Appearance of polymorphs after irradiation

Fig. 2 shows the time courses for discoloration of carbamazepine under near-UV fluorescent light at 45°C, 31% r.h. The surface of all pelleted crystalline forms gradually turned

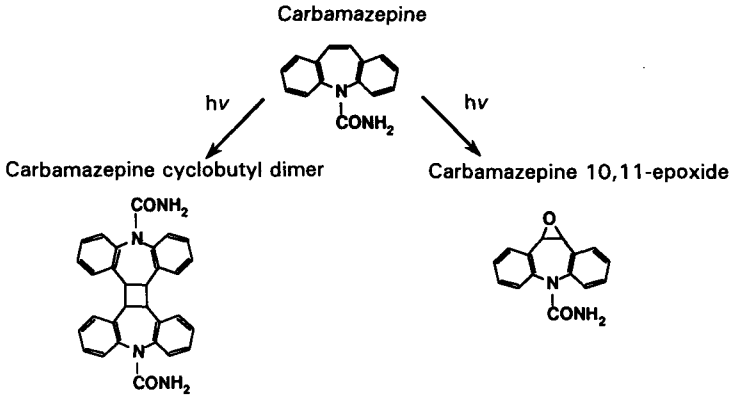

FIG. 4. Photodegradation products of carbamazepine.

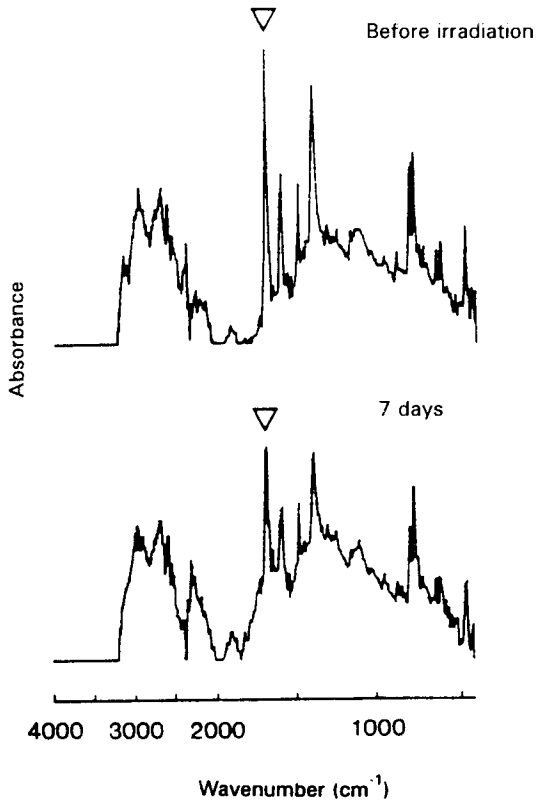

FIG. 5. FT-IR-RAS spectra of carbamazepine before and after irradiation.

from white to yellow-orange upon exposure, but did not change in the dark; the colour changes of all forms became more intense with increasing time of exposure to light irradiation. The ΔE values of forms I and III were 26·3 and 30·8, respectively, after irradiation for 7 days at 12·0 J cm^{-2} s^{-1}, but that of form II was 42·4, and the rate at which form II darkened was faster than that of forms I and III, indicating that form II was more unstable than forms I and III. The ΔE values of all forms increased with increasing irradiation energy. These results also suggested that the discoloration rate depended on the irradiation energy.

Solid-state photodegradation of polymorphs investigated by HPLC

Fig. 3 shows a typical HPLC chromatogram of carbamazepine after irradiation; several peaks were attributable to photoproducts and were identified as carbamazepine, its 10, 11-epoxide and its cyclobutyl dimer (Fig. 4), as judged by retention times of authentic standards and the UV spectral data obtained from the photodiode array detector.

Evaluation of photodegradation on the surface of carbamazepine polymorphs

Fig. 5 shows the FT-IR-RAS spectra of carbamazepine form II before and after fluorescence irradiation at 45°C, 31% r.h. The absorption peak at 1685 cm^{-1} attributable to the C=O stretch vibration of the carbonyl group decreased significantly after irradiation. This suggested that the residual carbamazepine on the pellet surface was decreased by degradation.

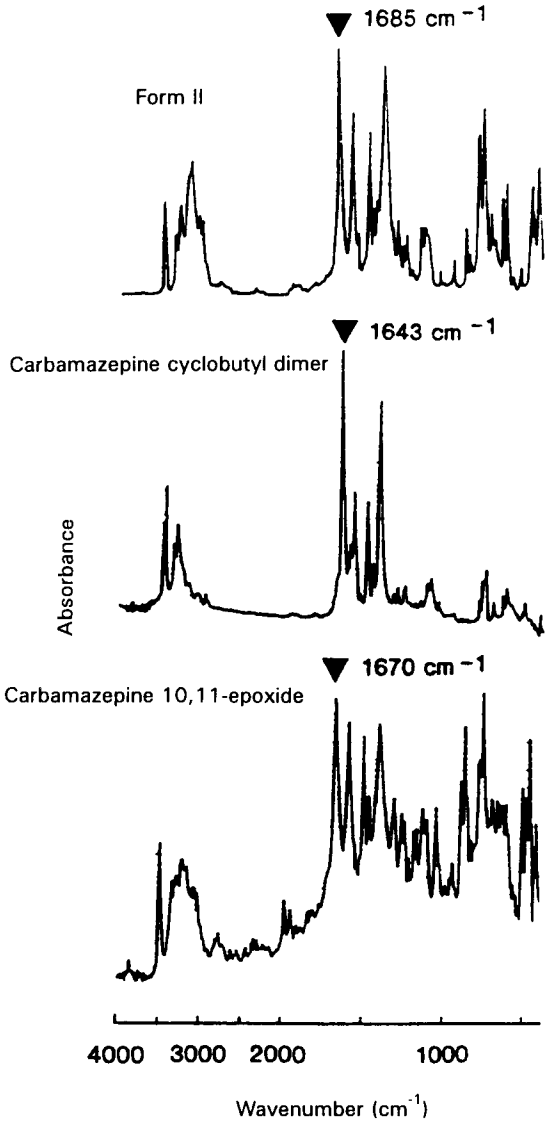

FIG. 6. FT-IR spectra of carbamazepine and its photodegraded products.

Fig. 6 shows the FT-IR spectra of carbamazepine, the cyclobutyl dimer and the 10, 11-epoxide. The bands attributable to the carbonyl group of forms I, II and III carbamazepine were at 1675, 1685 and 1683 cm^{-1}, and those of cyclobutyl dimer and 10, 11-epoxide were at 1643 and 1670 cm^{-1}, respectively. Therefore, we used the absorption of the C=O stretch band to evaluate the photodegradation.

Fig. 7 shows the calibration curves from FT-IR-RAS based on the peak at 1675 cm^{-1} of standard carbamazepine form I. The carbamazepine content on the surfaces of all forms was evaluated based upon calibration curves obtained from the appropriate form.

Solid-state photodegradation kinetics of polymorphs of carbamazepine

Fig. 8 shows a semilogarithmic plot of the degradation profiles of various polymorphs under irradiation by near-UV fluorescent lamp at 45°C, 31% r.h. Straight lines were

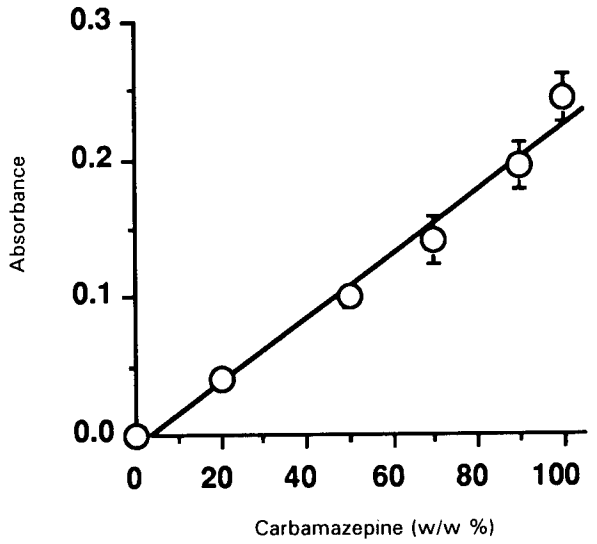

FIG. 7. Calibration curves based upon the absorption at 1685 cm^{-1} in FT-IR-RAS.

obtained for each crystalline form, including the induction period, indicating that degradation of the drug on the surface followed first-order kinetics. The degradation rate constant and the induction period were estimated from the linear part of the plots by the least-squares method.

Table 1 shows the induction period and the degradation rate constants for solid-state photodegradation of various polymorphs. The induction periods of all forms were not significantly different, and those by irradiation at 12·0 J cm^{-2} s^{-1} were slightly shorter than those at 3·0 J cm^{-2} s^{-1}, respectively; all degradation started after irradiation for 1 day. However, the degradation rate constant of form II at 12·0 J cm^{-2} s^{-1} was 5·1- and 1·5-fold those of forms I and III, respectively. The order of polymorphs estimated by FT-IR-RAS method agreed with that by the colorimetric measurement, indicating that the discoloration reflected the surface decomposition. In general, the chemical stability of polymorphs on the surface was significantly different. Kaneniwa et al (1987) estimated that the heat of solutions of carbamazepine forms I, II and III was 9·28, 7·86 and 10·6 kcal mol^{-1}, respectively, in distilled water, based upon the dissolution kinetics equation using the rotating disk method, and that the solubilities at 50°C of forms I, II and III were 1260, 959 and 1017 μg mL^{-1}, respectively. The order of the heat of solution of carbamazepine polymorphs was III ≥ I > II, but that of the solubility at 50°C was I > III > II. Since our experiments were performed at 45°C, the solid-state photoreactivity of the polymorphs is probably responsible for their solubility or heat of solution. On the other hand, Kaneniwa et al (1984) also reported that form II was the most hygroscopic, and the order of the hygroscopicity of the polymorphs was II > III > I. Since the order of the photostability of carbamazepine polymorphs was the same as that of the hygroscopicity, it is considered that the adsorbed water on the surface acts as a catalyst for the reaction.

Table 1. The degradation rate constants and induction periods for solid-state photodegradation of carbamazepine polymorphs.

Form	Irradiation intensity (J m^{-2} s^{-1})	Induction period (days)	Degradation rate constant (day^{-1})	Discoloration after 7 days at 45°C (ΔE)
I	3·0	1·17	$1·12 \times 10^{-2}$	21·7
	12·0	0·96	$2·40 \times 10^{-2}$	26·3
II	3·0	1·36	$9·78 \times 10^{-2}$	35·2
	12·0	1·20	$1·27 \times 10^{-1}$	42·4
III	3·0	1·37	$6·10 \times 10^{-2}$	22·8
	12·0	1·21	$7·11 \times 10^{-2}$	30·8

The degradation rate constants of forms I, II and III at 12 J cm^{-2} s^{-1} were respectively 48, 30 and 16% greater than those at 3·0 J cm^{-2} s^{-1}. It is suggested that the degradation rate of carbamazepine polymorphic forms is accelerated by the irradiation energy, but the effect was not so significant.

Relationship between the degradation of carbamazepine polymorphs and ΔE

Fig. 9 shows the relationships between ΔE and decomposition of polymorphs at 3·0 and 12·0 J cm^{-2} s^{-1}. The slope of form II was the largest and the order was II > I > III,

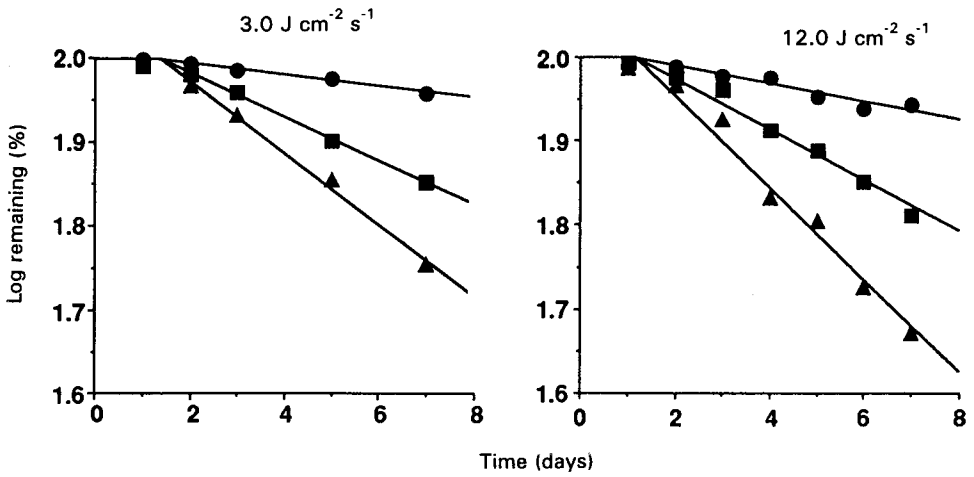

FIG. 8. The apparent first-order plots for solid-state photodegradation of carbamazepine polymorphs at various irradiation intensities under near-UV fluorescent light. ● I, ▲ II, ■ III.

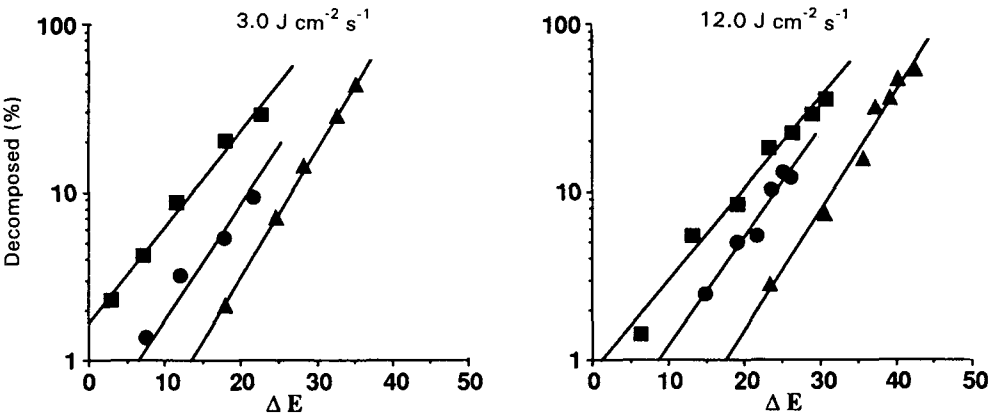

FIG. 9. Relationship between colour difference (ΔE) and percent decomposition of carbamazepine polymorphs. ● I, ▲ II, ■ III.

indicating that the crystalline state affects the photoreactivity of carbamazepine; however, the slope of each form at 3·0 J cm^{-2} s^{-1} was the same as that at 12·0 J cm^{-2} s^{-1}. The results suggested that the ΔE of the sample pellets of polymorphs after irradiation reflected the solid-state photodegradation. Therefore, the regression lines could be represented by equation 1, and the amount of decomposed carbamazepine (C_d) on the sample pellet surface was evaluated as:

$$\log C_d = K\,\Delta E + B \qquad (1)$$

where K and B are constant.

The results suggested that surface decomposition can be estimated using the ΔE value obtained by colorimetric measurement.

We conclude that FT-IR-RAS is a useful non-invasive method for evaluating the drug content on the surface of pharmaceutical preparations, and that colour difference values can also be used to evaluate surface decomposition.

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