

Effect of Titanium Dioxide on Photostability of Solid-State Mequitazine

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TiO₂ has been widely used in pharmaceutical products, and it also has been used as a photocatalyst. In this study, the influence of photocatalytic activity on the stability of solid-state mequitazine, an H₁-blocker, was investigated. The photo-degradation of mequitazine with TiO₂ occurred under irradiation with both light sources. The degree of degradation of mequitazine with anatase was higher than that of rutile. The degradation was significantly enhanced with increasing relative humidity. The relationship between the apparent degradation rate constant and water vapor pressure could be clearly described by a simple power law. The major photo-degradation products of mequitazine, resulting from photocatalytic activity of TiO₂, were mequitazine-S-oxide and mequitazine-sulphone. A remarkable degradation of mequitazine occurred with addition of TiO₂, and its photocatalytic activity was controlled by water vapor pressure. The photo-degradation of mequitazine with TiO₂ is a different process from mequitazine without TiO₂, because mequitazine-S-oxide and mequitazine-sulphone are not formed with normal photo-degradation of mequitazine.

Key words preformulation; solid state stability; photostability; titanium dioxide; photocatalytic activity

Titanium dioxide (TiO₂) is known as a useful inorganic pigment and is widely used as a coating material for solid pharmaceutical preparations. Recently, many studies have been performed, from a material science perspective, to modify the function of TiO₂ as a strong photocatalyst. In some studies the photocatalytic activity of TiO₂ has been linked to oxidation-reduction reactions.^{1–6)}

With regard to pigment use, TiO₂ is usually surface-treated to prevent photocatalytic activity. On the other hand, for pharmaceutical use, TiO₂ is not surface-treated, and even if the surface is treated, the amount of surface coating substance would be very small, because of its strictly regulated purity. Thus, TiO₂ for pharmaceutical use may exhibit considerable photocatalytic activity. Therefore, when TiO₂ is used in pharmaceutical preparations, some drugs may often be easily decomposed by light irradiation. However, on pharmaceutical research field, almost studies were reported for the effect of light resistance of TiO₂ or the reaction related to TiO₂ in the solution system.^{7–11)} We focused the solid-state reaction between TiO₂ and drug substance. In our previous work, it was revealed that famotidine, known as an H₂-blocker, with TiO₂ as an additive, was easily discolored by only light, and the photocatalytic activity of TiO₂ was controlled by relative humidity.¹²⁾ Therefore, the purpose of this preformulation study is to clarify the relationship between the addition of TiO₂ and drug decomposition, so that from a thorough investigation, consistently high quality in pharmaceutical products may be assured.

Mequitazine, known as a histamine H₁-receptor antagonist, is slightly discolored under irradiation with light. On the basis of this fact, mequitazine may be unstable under light irradiation, and therefore it may be presumed that the photostability of mequitazine will be influenced by the photocatalytic activity of TiO₂. In this study, mequitazine was employed as a model drug for fundamental study and the effect of photocatalytic activity of TiO₂ on the solid-state photostability of mequitazine under various relative humidity conditions was investigated. The photodegradation products of ir-

radiated mequitazine containing TiO₂ were also investigated.

Experimental

Materials Two commercially available crystal structures of TiO₂, anatase and rutile, were used. In order to examine the effect of TiO₂ on photodegradation of mequitazine, the surface of these TiO₂ powders was not coated with any material. The anatase and rutile forms of TiO₂ were supplied by Toho Titanium Co., Ltd. and Showa Chemical Co., Ltd, respectively. Mequitazine was obtained from Sumika Fine Chemicals Co., Ltd. Mequitazine-N-oxide and mequitazine-S-oxide were obtained from Azwell Inc. All other chemicals and reagents were analytical grade.

Discoloration Test The samples used for the discoloration test were prepared as follows: Mequitazine and TiO₂ were physically mixed in a bowl at a mass ratio of 1 : 1. A 200 mg sample of mixture was compressed into a 10 mm diameter pellet under a compression force of 10 kN, using an accurate compression/tension testing machine (Autograph model IS-5000, Shimadzu).

Samples were placed in a light-irradiation tester (LIGHTTRON LT-120, Nagano Science) at 25 °C and irradiated with a D65 lamp (illuminance: 3500 lx). Discoloration of the pellet surface, after irradiation, was measured using a chromameter (Model 300A, Nippon Denshoku) after the designated time points in the Lab color system.

Degradation Test The samples for the degradation test were prepared as follows: Mequitazine was dissolved in methanol (1 mg/ml) and 50 μl of the solution was added to 10 mg of TiO₂ powder. After thorough dispersion, this suspension was dried under vacuum. A solution of benzophenone in isooctane-methanol (1 : 1 v/v) was prepared as an internal standard for high-performance liquid chromatography (HPLC) analysis.

Each sample was placed in a desiccator at 0, 22, 75 and 97% RH at 25 °C and irradiated with a near-UV lamp (irradiation energy: 1.0 mW/cm²) or a D65 lamp (illuminance: 3500 lx) in the light-irradiation tester (LIGHTTRON LT-120, Nagano Science). The amount of mequitazine remaining in the sample, with respect to time, was measured by HPLC. A relative humidity of 0% RH was maintained using diphosphorus pentoxide, and others were adjusted using saturated aqueous solutions of several inorganic salts; 22% RH: potassium acetate, 75% RH: sodium chloride, and 90% RH: potassium sulfate.

HPLC Analysis Mequitazine was analyzed using an HPLC system consisting of a solvent delivery system (Model 510, Waters) and a UV detector (Model 484, Waters) at a detection wavelength of 254 nm, or a photodiode array detector (Model 996, Waters) at wavelengths of 250–360 nm. The prepacked column (Zorbax Rx-SiL, 5 μm, 4.6×250 mm, Agilent Technologies) was operated at room temperature with a flow rate of 1.5 ml/min. The mobile phase consisted of isooctane : ethanol : acetonitrile : isopropylamine : water (120 : 100 : 15 : 7 : 2 volume ratio). After irradiation, each sample was dissolved in the internal standard solution and after filtrated by

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0.45 μm membrane filter, a 20 μl aliquot was injected into the chromatograph.

HPLC/APCI-MS Analysis Degradation products of mequitazine were completely identified by a high-performance liquid chromatography/atmospheric pressure chemical ionization-mass spectrometry (HPLC/APCI-MS) system. The HPLC system consisted of a solvent delivery system and a UV detector (LC-10Avp system, Shimadzu). The prepacked column (Lichrospher CN, 5 μm , 4 \times 125 mm, Cica-Merk) was operated at room temperature with a flow rate of 1.8 ml/min. The mobile phase consisted of acetonitrile : methanol : isopropanol : water : 1 M ammonium acetate solution (85 : 5 : 5 : 6.65 : 0.35 volume ratio). The sample preparation was the same as that described previously for the HPLC analysis.

Mass spectrometric detection was achieved by means of an Applied Biosystems API 3000 apparatus using an APCI interface. MS measurements were acquired in positive ion, full scan modes from 100 to 400, using a fragmentation voltage of 80 V to determine the molecular weights of the degradation products.

Results

Figure 1 shows the effect of TiO_2 on the time course of surface discoloration for the mequitazine pellet at 25 $^\circ\text{C}$. Mequitazine with a TiO_2 additive, for both crystal structures, was significantly discolored; whereas, without TiO_2 , only slight discoloration was observed, even after a long period of irradiation (25 h). Discoloration of mequitazine with anatase additive was significantly greater than that with rutile. Figure 2 shows the effect of TiO_2 on the degradation of mequitazine with time at 25 $^\circ\text{C}$ and 75% RH. Under irradiation with both the near-UV and D65 lamps, mequitazine with anatase

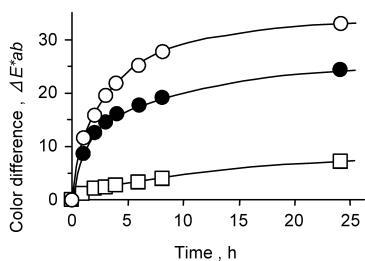


Fig. 1. The Effect of Photocatalytic Activity of TiO_2 on the Discoloration of Mequitazine at 25 $^\circ\text{C}$ under Irradiation by a D65 Lamp
(\circ) With anatase, (\bullet) with rutile, and (\square) without TiO_2 .

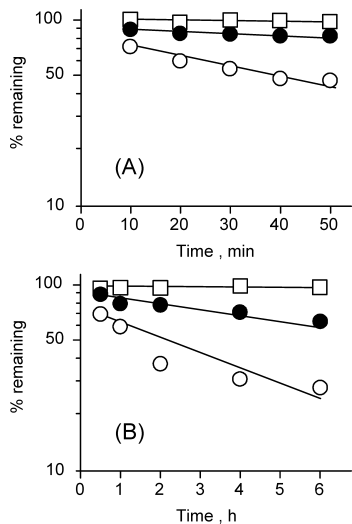


Fig. 2. The Effect of Photocatalytic Activity of TiO_2 on the Degradation of Mequitazine at 25 $^\circ\text{C}$ and 75% RH and under Irradiation by (A) a Near-UV Lamp and (B) a D65 Lamp
(\circ) With anatase, (\bullet) with rutile, and (\square) without TiO_2 .

showed a remarkable degradation, but was only slightly degraded for rutile. Mequitazine without TiO_2 was hardly degraded, even after a long period of irradiation. The degradation rate of mequitazine was much higher under the near-UV lamp, than under the D65 lamp. This degradation process apparently followed a first order reaction. Figure 3 shows the degradation of mequitazine with TiO_2 with respect to time, at various relative humidity, with irradiation using near-UV light. The degree of degradation increased with increasing relative humidity for both TiO_2 crystal forms, and particularly for anatase, the increment of degradation was greater. The phenomenon for irradiation observed under the near-UV lamp was also observed under the D65 lamp (Fig. 4). Figure 5 shows the semi-logarithmic plots of the relationship between the apparent degradation rate constant, calculated from the slopes of regression lines in Figs. 3 and 4, and the water vapor pressure, converted from relative humidity, under each

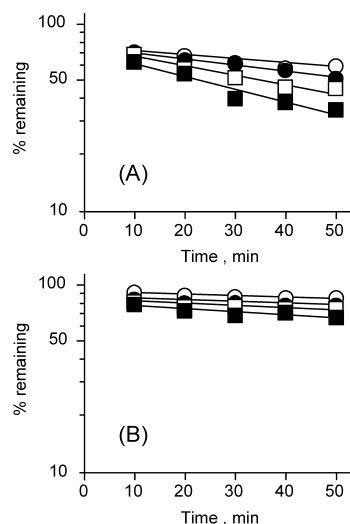


Fig. 3. The Effect of Relative Humidity on the Degradation of Mequitazine at 25 $^\circ\text{C}$ under Irradiation by a Near-UV Lamp: (A) with Anatase; and (B) with Rutile
(\circ) 0% RH, (\bullet) 22% RH, (\square) 75% RH, (\blacksquare) 97% RH.

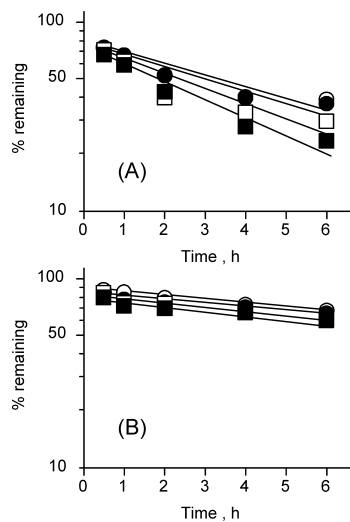


Fig. 4. The Effect of Relative Humidity on the Degradation of Mequitazine at 25 $^\circ\text{C}$ under Irradiation by a D65 Lamp: (A) with Anatase; and (B) with Rutile
(\circ) 0% RH, (\bullet) 22% RH, (\square) 75% RH, (\blacksquare) 97% RH.

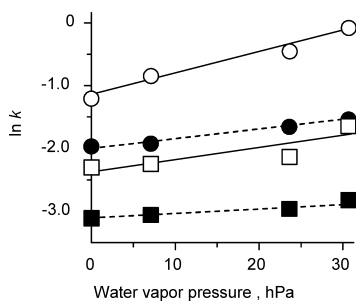


Fig. 5. The Effect of Water Vapor Pressure on the Degradation Rate Constant

(○) With anatase under irradiation by a near-UV lamp and (●) with anatase under a D65 lamp; (□) with rutile under irradiation by a near-UV lamp and (■) with rutile under a D65 lamp.

Table 1. r -Values under the Various Irradiation Conditions

Light source	$r (\times 10^3)$	
	Anatase system	Rutile system
Near-UV lamp	33.5	18.0
D65 lamp	14.0	8.2

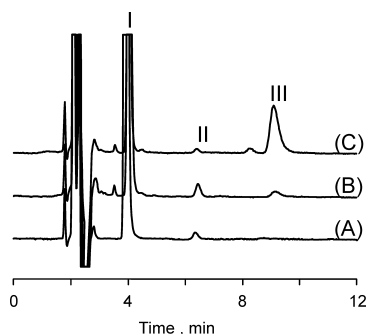


Fig. 6. HPLC Chromatograms of the Sample after 50 min Irradiation by a Near-UV Lamp at 25 °C and 97% RH; (A) Mequitazine, (B) Mequitazine with Rutile, (C) Mequitazine with Anatase

Each peak is assigned as (I) mequitazine, (II) mequitazine-*N*-oxide and (III) mequitazine-*S*-oxide.

light source. Good linear relationships were established between the logarithm of the apparent degradation rate constant and the water vapor pressure, for either of the TiO₂ crystal forms. The apparent degradation rate constant for anatase was larger than that for rutile, at all water vapor pressures under any of the light sources. This fact clearly indicates that anatase exhibits higher photocatalytic activity than rutile. These results imply a relationship between the apparent degradation rate constant and water vapor pressure as shown in Eq. 1

$$\ln k = \ln k_0 + r \cdot P \quad (1)$$

where P is the water vapor pressure, r is a coefficient relating to water vapor pressure dependency of the apparent degradation rate constant, and k_0 is the apparent degradation rate constant calculated for 0% RH. The values of r , calculated from Eq. 1, are given in Table 1.

Figure 6 shows the HPLC chromatograms of samples after 6 h irradiation with the D65 lamp at 25 °C and 97% RH. Each of the peaks I, II and III were identified to be

Table 2. UV and HPLC Characteristics of Mequitazine and Related Compounds

Peak	Compound	Retention time (min)	Maximum UV absorbance (nm)
I	Mequitazine	4.03	308
II	Mequitazine- <i>N</i> -oxide	6.45	308
III	Mequitazine- <i>S</i> -oxide	9.12	278, 300, 346

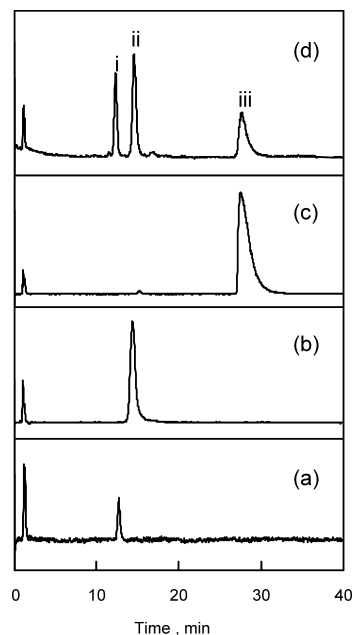


Fig. 7. HPLC Chromatograms for MS Analysis of the Standard with (a) Mequitazine, (b) Mequitazine-*N*-oxide, (c) Mequitazine-*S*-oxide and (d) Mequitazine with Anatase after 50 min Irradiation by a Near-UV Lamp at 25 °C and 97% RH

mequitazine, mequitazine-*N*-oxide and mequitazine-*S*-oxide, respectively, by their UV spectrum. The characteristics of each peak obtained from the HPLC chromatograms and UV spectra are shown in Table 2. Interestingly, degradation of mequitazine without TiO₂ produced only mequitazine-*N*-oxide as the degradation product; however, mequitazine with TiO₂ gave two kinds of degradation products; mequitazine-*N*-oxide and mequitazine-*S*-oxide.

The degree of mequitazine-*S*-oxide formation for mequitazine with anatase was particularly larger than that for rutile. HPLC/APCI-MS analysis was used as another approach to identify the photodegradation products. The condition for the HPLC-MS was not the same as that described for the HPLC analysis, because the degradation products could not be ionized under the former condition. Figure 7 shows the chromatograms of these photo degradation products. The m/z value of each peak was determined by MS analysis, as shown in Fig. 8. The retention time on the chromatogram and the m/z value of the peak (d)-i correspond to that of intact mequitazine, and peak (d)-iii corresponds to that of the standard sample of mequitazine-*S*-oxide. On the contrary, the retention time and the m/z value of peak (d)-ii did not correspond to that of the standard sample of mequitazine-*N*-oxide. From the results of previous reports,¹³⁾ (d)-ii was presumed to be mequitazine-sulphone, because the m/z value (355.4) of the (d)-ii peak coincided with that of mequitazine-sulphone.

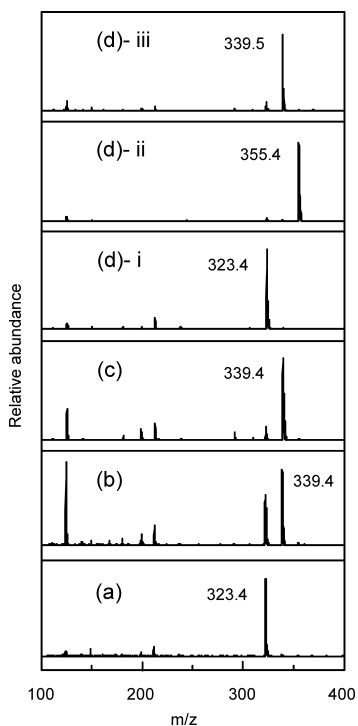


Fig. 8. Mass Spectroscopic Peaks Obtained from HPLC Chromatography cf. Fig. 7.

At this retention time, mequitazine-*N*-oxide could not be detected, due to the difficulty of ionizing mequitazine-*N*-oxide under these HPLC-MS analysis conditions. According to these results, it was confirmed that at least three kinds of photo-degradation products, mequitazine-*N*-oxide, mequitazine-*S*-oxide and mequitazine-sulphone were formed from mequitazine.

Discussion

Mequitazine, with the addition of TiO_2 , was easily degraded by light irradiation. The degree of degradation for mequitazine with anatase was larger than that with rutile, under all experimental conditions. This fact can lead to the conclusion that the photocatalytic activity of anatase is higher than that of rutile. The photocatalytic activities of these TiO_2 phases have been measured by a direct electrochemical measuring method, four-probe method.¹²⁾ The degradation of mequitazine occurred under irradiation with not only a near-UV lamp, but also a D65 lamp. The rate of degradation of mequitazine with a near-UV lamp was faster than that with a D65 lamp for both crystal forms because the energy giving an excitation state of a near-UV lamp would be stronger than that of a D65 lamp. Since D65 lamps have been widely used as a standard light source for the light stability test, the quality of pharmaceutical preparations containing photo-labile drugs such as mequitazine with TiO_2 , are easily-deteriorated by light irradiation. The degradation of mequitazine with TiO_2 was remarkably enhanced by an increase of relative humidity. The relationship between water vapor pressure and the apparent degradation rate constant could be described by a simple power law. Since the same tendency was observed in our previous study,¹²⁾ this fact suggests that the photocatalytic activity of the two TiO_2 phases is controlled by water vapor pressure. Furthermore, during the

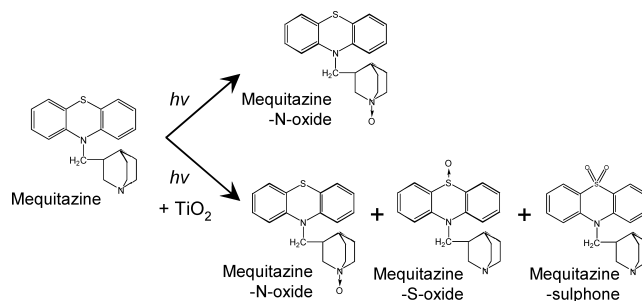
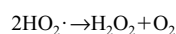
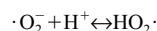
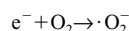
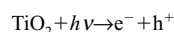


Fig. 9. Degradation Scheme of Mequitazine and Mequitazine with TiO_2 upon Exposure to Light

degradation process, the ratio of the *r*-value for anatase to that for rutile, under the near-UV lamp, was calculated to be 1.71. This value was similar to that under the D65 lamp, calculated as 1.86. This result also suggests that the dependency of the ratio of the *r*-value for anatase to that for rutile on water vapor pressure would be almost constant, even under a different type of light source.

Three kinds of photodegradation products of mequitazine were detected in this study; mequitazine-*N*-oxide, mequitazine-*S*-oxide and mequitazine-sulphone. It was confirmed that mequitazine-*N*-oxide was a direct photooxidation product of mequitazine, because it was obtained by light irradiation of pure mequitazine, without TiO_2 .¹⁴⁾ On the other hand, mequitazine-*S*-oxide and mequitazine-sulphone were photocatalytic degradation products after irradiation of mequitazine with TiO_2 additive. According to these results, the following degradation mechanism may be possible: The degradation caused by photocatalytic activity of TiO_2 would predominantly oxidize the sulfur part of the mequitazine molecule, as shown in Fig. 9. Mequitazine-sulphone has been reported as a degradation product of mequitazine reacted with hydrogen peroxide.¹³⁾ Some studies have described that the radicals are generated due to photocatalytic activity of TiO_2 .^{1,15,16)} In the series of radical reactions, the generation of hydrogen peroxide may be considered as follows:



Moisture proofing is important to restrain the photocatalytic activity of TiO_2 in pharmaceutical preparations of photo-labile drugs, because moisture can play an important role in the degradation reaction.

Conclusion

Mequitazine was significantly degraded by photocatalytic activity of TiO_2 under light irradiation and this degradation was enhanced by increasing the relative humidity under various storage conditions. Because the relationship between the relative humidity and the apparent degradation rate constant was described with a simple power law, the photocatalytic activity of TiO_2 was confirmed to be controlled by moisture adsorption onto mequitazine crystals. The degradation products of mequitazine with TiO_2 were different from that formed from mequitazine without TiO_2 . By the interaction between

TiO₂ and mequitazine, unexpected photo-degradation products could be identified. So using TiO₂ for pharmaceutical products, we must be care of unexpected photo-degradation products from ingredient.

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