

Effect of Relative Humidity on the Photocatalytic Activity of Titanium Dioxide and Photostability of Famotidine

K. KAKINOKI,¹ K. YAMANE,¹ R. TERAOKA,² M. OTSUKA,² Y. MATSUDA²

¹Manufacture Technology Department, Taiho Pharmaceutical Company, Ltd., 224-2, Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-0194, Japan

²Department of Pharmaceutical Technology, Kobe Pharmaceutical University, 4-19-1, Motoyama-Kitamachi, Higashi-Nada, Kobe 658-8558, Japan

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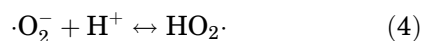
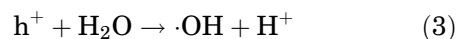
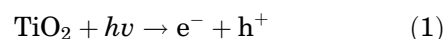
ABSTRACT: Titanium dioxide (TiO₂) has been widely used as a pharmaceutical excipient and is also known to be a strong photocatalyst. An investigation into the relationship between the photocatalytic activity of TiO₂ and the photostability of famotidine, which is known as an H₂-blocker, is presented. The photocatalytic activity of the anatase form of TiO₂, as measured by the four-probe method, is ~1.5 times higher than that of the rutile form. Discoloration of famotidine in a binary system containing TiO₂ depends significantly on both the wavelength of the irradiating light and the crystal form of the TiO₂, with the degree of discoloration of anatase higher than that of the rutile form. Discoloration of famotidine also depends on relative humidity. The relationship between discoloration rate constant and water vapor pressure is linear. These results demonstrate that famotidine is easily discolored by the photocatalytic activity of TiO₂ and suggest that the solid-state photocatalytic activity of TiO₂ is strongly affected by relative humidity. © 2004 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 93:582–589, 2004

Keywords: preformulation; physical stability; excipients; polymorph; materials science; TiO₂

INTRODUCTION

Titanium dioxide (TiO₂) has been known to be an effective inorganic pigment for a long time. Recently, TiO₂ has come to be widely used in many industries, including cosmetics, food additives, pharmaceuticals, and environment purification. In particular, over the last several decades, TiO₂ has been considered by many material scientists to be a strong photocatalyst.¹ In some studies about the photocatalysis of TiO₂, the solid-state photocatalytic activity of TiO₂ has been linked to oxidation–reduction reactions by some kind of moisture-derived radicals between the substrate

and TiO₂. A possible mechanism for the formation of these radicals is the following series of reactions:^{1–7}



In these chemical reactions, e[−] and h⁺ represent electrons and positive holes, respectively. Because of their photocatalytic properties, TiO₂ particles used as an inorganic white pigment instead of a catalyst are usually coated with hydroxylate metals to prevent generation and reaction of radicals by photocatalytic activity. However, coating

Correspondence to: Koichi Kakinoki (Telephone: 81 886 65 6054; Fax: 81 886 65 7995; E-mail: k-kakinoki@taiho.co.jp)

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the surface of TiO₂ particles reduces the chemical purity, and the purity of TiO₂ for pharmaceutical use is strictly regulated. The Japanese Pharmacopoeia requires >98.5% purity, and the United States Pharmacopoeia, requires >99.0% purity. As a result, the surfaces of TiO₂ particles for pharmaceutical use are not coated, and even if they were coated, the amount of hydroxylate metal would need to be very small. Thus, TiO₂ for pharmaceutical use is expected to exhibit photocatalytic activity. In spite of these facts, when TiO₂ is used in pharmaceutical products, no measures are taken in terms of protection from light and/or mutual reactions between drugs with which TiO₂ acts as a photocatalyst. Some drugs are often easily decomposed by light. So, evaluation of the photostability of these pharmaceuticals is required to assure consistently high quality. Therefore, when TiO₂ is used in pharmaceutical formulations, the photocatalytic activity of TiO₂ and interactions between the drug and TiO₂ must be investigated.

Famotidine, which is known as an H₂-blocker, is stable under irradiation by light, but in the presence of TiO₂ was observed to undergo remarkable discoloration during preliminary studies. This discoloration appears to have been due to the photocatalytic activity of TiO₂, with famotidine decomposed and discolored by photocatalytic reactions involving TiO₂. An investigation into the relationship between the photocatalytic activity of TiO₂ and the photostability of famotidine was thus conducted.

EXPERIMENTAL

Materials

Two commercially available crystal forms of TiO₂ were used; they are the anatase form and the rutile form. Surfaces of the TiO₂ particles were not coated with any material to examine the effect of only TiO₂ on famotidine. The specific surface areas of the anatase and rutile forms were 14.6 and 7.8 m²/g, respectively, as determined by gas adsorption measurements (Flowsorb II model 2300, Shimadzu Company). The anatase form was supplied by Toho Titanium Company, Ltd., and the rutile form was supplied by Showa Chemical Company, Ltd. The famotidine was obtained from Nippon Bulk Yakuhin Company, Ltd. All other chemicals and reagents were analytical grade.

Binary mixtures of famotidine and TiO₂ were prepared as compacts without coatings for light irradiation testing. Powder mixtures were used to increase the contact probability of famotidine and TiO₂ particles as much as possible to facilitate discoloration of the famotidine, because the photo-reaction between TiO₂ and famotidine relies on solid contact. Compacts were prepared by physically mixing famotidine and TiO₂ in a bowl at a mass ratio of 4:1. Mixtures of 25 mg of mass were compressed into 10-mm diameter, 1-mm thick compacts under a compression force of 10 kN using an accurate compression/tension testing machine (Autograph model IS-5000, Shimadzu Company).

Measurement of the Photocatalytic Activity of TiO₂

Before investigating the effects of the addition of TiO₂ on discoloration of famotidine, a method for measuring the photocatalytic activity of TiO₂ different than previously reported methods was developed.²⁻⁶ The existing methods tend to be concerned with the degradants of substances photocatalyzed by TiO₂ under limited conditions. Our approach is based on direct detection of the electrochemical reactions caused by the photocatalytic activity of TiO₂. The four-probe method was successfully applied to these reactions as a direct measurement method.

A schematic of the experimental setup of the four-probe method is shown in Figure 1. TiO₂ (1% w/v) was dispersed in a 0.1% w/v aqueous solution of sodium hydrogen carbonate. The two pairs of probes were placed in this solution, with one pair linked to a voltmeter and the other to a

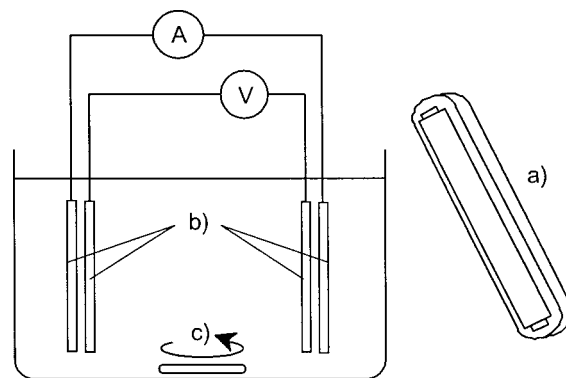


Figure 1. Experimental setup (four-probe method) for measuring photocatalytic activity of TiO₂. Key: (A) current source; (V) voltmeter, (a) near-UV lamp; (b) indium ingot probes; (c) stirring bar.

current source. The solution was stirred with a magnetic stirrer. The electric resistance of the solution was calculated by measuring the voltage at constant current.

As already described, radicals are produced by the photocatalytic activity of TiO_2 . By irradiating the solution with a near-ultraviolet (UV) lamp (irradiation energy, 1.0 mW/cm^2), the electric resistance of the solution decreased as an increasing amount of radicals and ions were generated by photocatalytic activity of the TiO_2 . This decrease in the electric resistance was thought to be due to the photocatalytic activity of TiO_2 .

Measurement of Discoloration

Discoloration of the surfaces of samples was determined by measuring color differences (ΔE^*ab) using a chromameter (CR-221, Minolta Company, Ltd.) in the $L^*a^*b^*$ color system.

Irradiation Tests

Effect of Wavelength

Experiments were conducted at room temperature and ambient relative humidity (RH) with a monochromatic light source. Wavelengths were selected in the range 300–450 nm with a grating monochromator (CRM-50, JASCO Company), with the energy of monochromatic light incident on the sample set to $1.8 \times 10^5 \text{ J/m}^2$. To set the same energy on the samples, the irradiation time was adjusted by the irradiation intensity for unit time defined by each wavelength.⁸ After irradiation, color differences were calculated from surface color measurements performed on the sample compacts before and after irradiation.

Discoloration of Famotidine

Samples were placed in an environment of 30°C and 75% RH and irradiated by near-UV light (irradiation energy, 1.0 mW/cm^2). Changes in the colors of the samples as irradiation progressed were measured at several intervals. RH was maintained with a saturated aqueous solution of sodium chloride.

Effect of RH

Samples were placed in desiccators at 30, 60, 75, and 90% RH at 30°C and irradiated with near-UV light (irradiation energy, 1.0 mW/cm^2). Changes in the colors of the samples as irradiation

progressed were measured at several intervals. RH was maintained with saturated aqueous solutions of several inorganic salts: 30% RH, magnesium dichloride hexahydrate; 60% RH, ammonium nitrate; 75% RH, sodium chloride; and 90% RH, potassium nitrate.

RESULTS

Measurement of Photocatalytic Activity

The changes in the electric resistance of an aqueous suspension of TiO_2 as measured by the four-probe method are shown in Figure 2. Significant reductions in relative resistance by light irradiation were observed for all types of TiO_2 . Relative resistances were scaled to define electrical resistances under no irradiation as 100%. The relative resistance in the dispersed anatase system was confirmed to decrease by 40% after 20 min of irradiation, whereas in the rutile system, resistance decreased by 65%. These results suggest that the photocatalytic activity of the anatase form is ~ 1.5 times higher than that of the rutile form.

Irradiation Test

Effect of Wavelength

Famotidine was stable in light with no pharmaceutical excipient present, but discolored dramatically in the presence of TiO_2 . The effect of wavelength on the discoloration of famotidine compacts is shown in Figure 3. The maximum color changes, which were easy to see with the

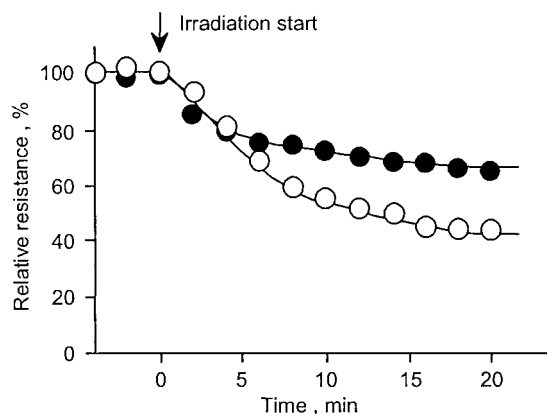


Figure 2. Photocatalytic activity of TiO_2 measured by the four-probe method. Key: (○) anatase form; (●) rutile form.

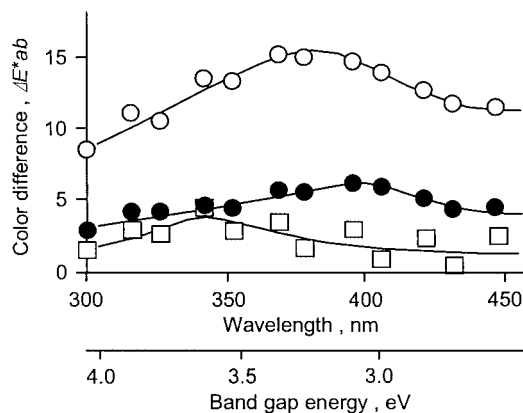


Figure 3. Effect of irradiating wavelength on the discoloration of famotidine compacts containing (○) the anatase form of TiO₂, (●) the rutile form of TiO₂, and (□) no TiO₂.

naked eye, were produced by 380 nm light in the anatase system and by 400 nm light in the rutile system. Discoloration of famotidine without the presence of TiO₂ was also observed at ~340 nm. The extent of this color difference (ΔE^*ab) was quite small and could not be distinguished visually.⁹

Band gap energy (E) is the crystal-form-dependent energy needed for photocatalytic activity. The band gap energies of the anatase and rutile forms of TiO₂ are 3.2 and 3.0 eV, respectively,^{1,10,11} and the relationship between band gap energy and wavelength of light is

$$E = hv = hc/\lambda \quad (5)$$

where h is Planck's constant, v is the frequency of light, c is the velocity of light, and λ is the wavelength of light. Using eq. 5, the wavelength of light corresponding to the band gap energy of the anatase form was calculated as ~380 nm and that of the rutile form was calculated as ~410 nm. These wavelengths are in good agreement with the wavelengths inducing the maximum color changes in the famotidine compacts for each TiO₂ crystal form. This agreement of results suggests that the discoloration of famotidine in the presence of TiO₂ was induced by photocatalytic activity of TiO₂.

Discoloration of Famotidine

The effect of TiO₂ on the discoloration of famotidine compacts with time at 30°C and 75% RH is shown in Figure 4. Famotidine compacts containing no TiO₂ were slightly discolored after a long period of irradiation (3 h). In comparison,

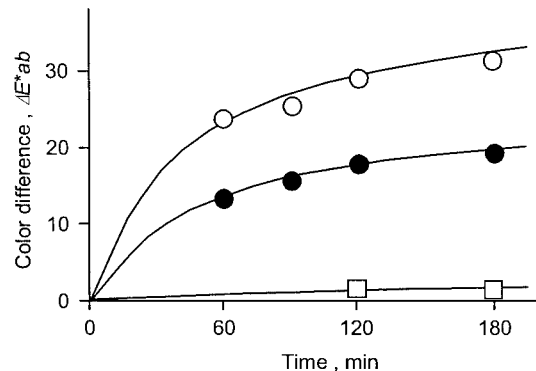


Figure 4. Effect of the photocatalytic activity of TiO₂ on the discoloration of famotidine at 30°C and 75% RH, for compacts containing (○) the anatase form of TiO₂, (●) the rutile form of TiO₂, and (□) no TiO₂.

famotidine compacts containing TiO₂ in any crystal form were discolored quite significantly. Changes in the color of famotidine compacts containing the anatase form of TiO₂ were much greater than those in compacts containing the rutile form.

To kinetically interpret the discoloration of famotidine compacts containing TiO₂, the following equation, reported by Matsuda et al.,¹² was applied to the discoloration process:

$$d(\Delta E^*ab)/dt = k(\Delta E^*ab)^n \quad (6)$$

where t is the irradiation time, k is the discoloration rate constant, and n is the reaction order. Integrating eq. 6 gives

$$\ln(\Delta E^*ab) = 1/(1-n) \cdot \ln[(1-n) \cdot k] + 1/(1-n) \cdot \ln t \quad (n \neq 1) \quad (7)$$

If the discoloration of famotidine compacts follows eq. 7, the relationship between irradiation time and color change could be established by a double-logarithmic plot. Double-logarithmic plots of the anatase and rutile systems shown in Figure 4 are presented in Figure 5. A clear relationship between discoloration and time was confirmed to exist, with parallel lines for the anatase and rutile forms. This result suggests that the kinetic model of eq. 6 could be applied to the discoloration of famotidine compacts containing TiO₂.

Effect of RH

The photocatalytic activity of TiO₂ has generally been known to be influenced by RH.¹³⁻¹⁷ The discoloration of famotidine compacts containing

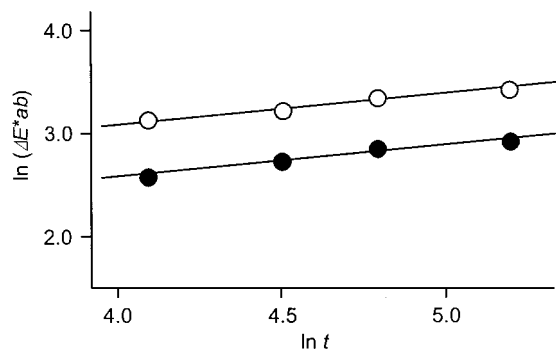


Figure 5. Double-logarithmic plots of the effect of photocatalytic activity of TiO_2 on the discoloration of famotidine compacts at 30°C and 75% RH, for compacts containing (\circ) the anatase form of TiO_2 and (\bullet) the rutile form of TiO_2 .

TiO_2 under various conditions of RH is plotted against time in Figure 6. The degree of color change increase significantly with increasing RH. On double-logarithmic plots of these discolorations, created with eq. 7, the slopes of lines calculated by the least squares method were 0.3–0.4 for the anatase form and 0.3–0.6 for the rutile form. The mechanisms of discoloration of famotidine compacts containing anatase and rutile forms are expected to be the same, because the photocatalysis by TiO_2 causes the same radical reactions, as already described. Thus, based on the same mechanism of radical reaction for both the anatase and rutile forms, all of the reaction orders are theoretically the same. Reaction orders were calculated from the slope of each line with eq. 7. A mean slope of 0.4 was obtained from the

eight lines. Lines with a fixed slope of 0.4 fit the data well, showing good agreement with all of the results (see Fig. 7). The y-intercept was then calculated as the arithmetic mean for each RH. The discoloration rate constants calculated with eq. 7 at each RH are given in Table 1. The RH values were converted to water vapor pressures to allow interpretations to be made based on a water content parameter. Semi-logarithmic plots of the relationship between discoloration rate constant and water vapor pressure are shown in Figure 8. Good linear relationships were established between the logarithm of discoloration rate constant and water vapor pressure for each of the crystal forms, with a correlation coefficient of 0.996 for the anatase form and of 0.971 for the rutile form. The discoloration rate constant of the anatase system was larger than that of the rutile system at all water vapor pressures, indicating the higher photocatalytic activity of the anatase form. These results imply a relationship between discoloration rate constant and water vapor pressure of

$$\ln k = \ln k_0 + r \cdot P \quad (8)$$

where P is water vapor pressure, r is a coefficient of relating water vapor pressure to discoloration rate constant, and k_0 is the discoloration rate constant at 0% RH. The values of r , calculated with eq. 8, are 3.55 for the anatase form and 5.57 for the rutile form. These results suggest that discoloration rate constant is significantly influenced by water vapor pressure in both crystal forms of TiO_2 . Thus, the photocatalytic activity of TiO_2 is dependent on RH. The relationship between RH and the ratio of the discoloration rate

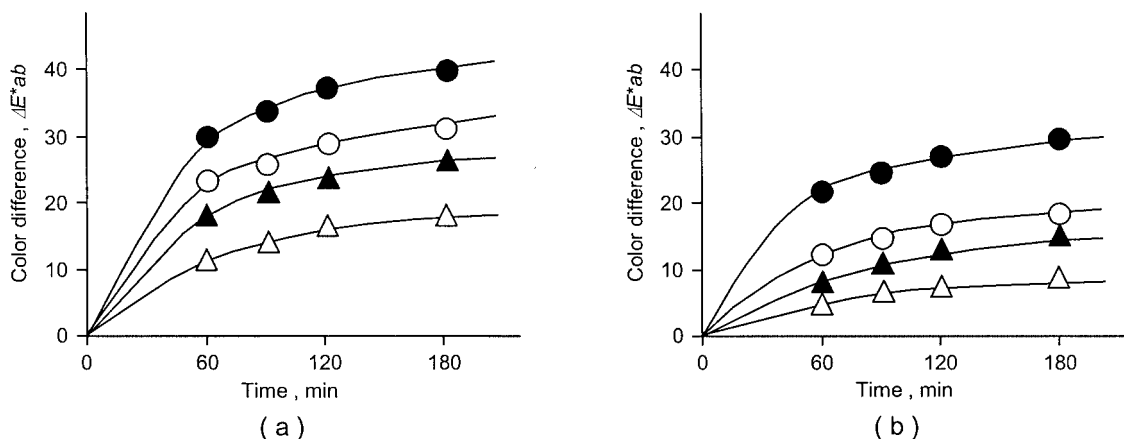


Figure 6. Effect of RH at 30°C on the discoloration of famotidine compacts containing (a) the anatase form of TiO_2 and (b) the rutile form of TiO_2 . Key: (\triangle) 30% RH; (\blacktriangle) 60% RH; (\circ) 75% RH; and (\bullet) 90% RH.

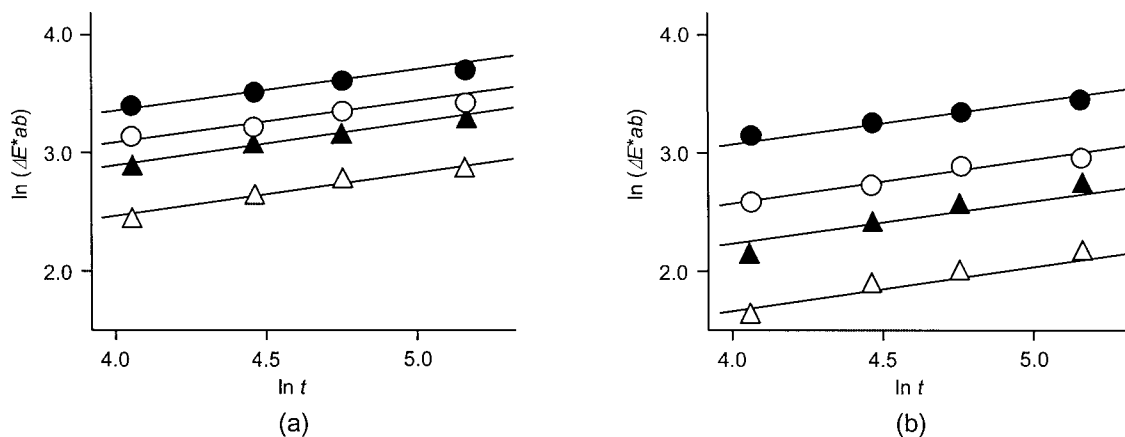


Figure 7. Regression lines with the same slope, as determined by double-logarithmic plots of the effect of RH at 30°C on the discoloration of famotidine compacts containing (a) the anatase form of TiO₂ and (b) the rutile form of TiO₂. Key: (△) 30% RH; (▲) 60% RH; (○) 75% RH; and (●) 90% RH.

constant of the anatase form to that of the rutile form is shown in Figure 9. The relationship is linear with a correlation coefficient of regression of 0.985. From the data in Figure 9, the ratio of the discoloration rate constant of the anatase form to that of the rutile form was estimated as ~ 1.5 at 100% RH. This result is in agreement with the ratio of the photocatalytic activity of anatase TiO₂ to that of rutile TiO₂ shown in Figure 2. The fact that the activity ratio at $\sim 100\%$ RH was almost equal to the ratio of photocatalytic activity of the anatase form to that of the rutile form in aqueous suspension verifies that the photocatalytic activity of TiO₂ is closely related to the photostability of famotidine compacts.

DISCUSSION

The photocatalytic activity of anatase measured by the four-probe method was ~ 1.5 times higher than that of rutile. This result is in agreement with the ratio of the discoloration rate constant of

Table 1. k Values under Various Relative Humidity Conditions

Relative Humidity (%)	k (min ⁻¹)	
	Anatase System	Rutile System
30	5.0	0.8
60	14.1	2.9
75	23.3	6.4
90	46.4	24.9

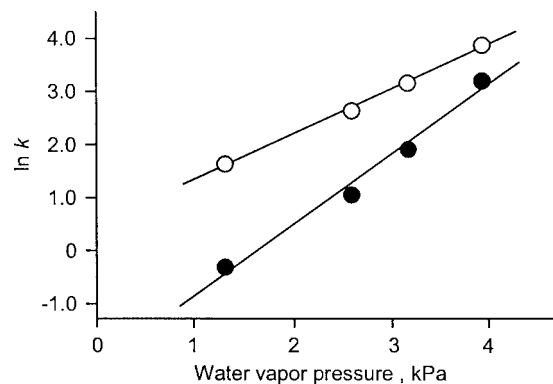


Figure 8. Semilogarithmic plots of the effect of water vapor pressure on discoloration rate constant for compacts containing (○) the anatase form of TiO₂ and (●) the rutile form of TiO₂.

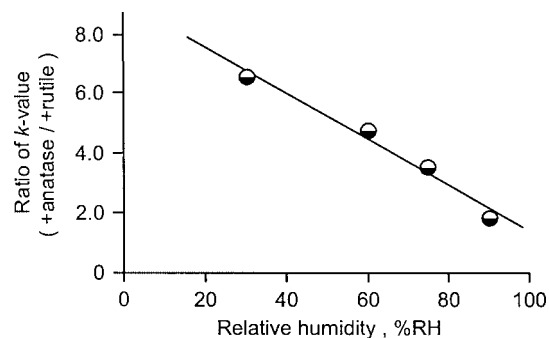


Figure 9. Relationship between the ratio of discoloration rate constants of anatase to rutile and RH ($y = -0.0762 \times +9.0804$; $r = 0.985$).

the anatase form to that of the rutile form at 100% RH. Differences in the degree of change in the appearance of famotidine compacts by adding TiO₂ are thus suggested to depend on differences in photocatalytic activity. Given this fact, the four-probe method has a possibility to be a benchmark technique for measuring the photocatalytic activity of TiO₂. Discoloration of famotidine compacts containing TiO₂ also depended on the wavelength of the irradiating light. Wavelengths corresponding to maximum discoloration correlated well with band gap energies for both TiO₂ crystal forms. This result suggests that discoloration was caused by solid-state reactions between famotidine and TiO₂ crystals. In addition, discoloration of famotidine compacts containing TiO₂ was enhanced by RH. Relationships between the RH and decomposition of drugs in the solid-state have been reported as very complex reaction models.^{18–21} However, the relationship found between the discoloration rate constant of famotidine compacts containing TiO₂ and water vapor pressure could be clearly described by a simple power law. Thus, RH is a major factor affecting the photocatalytic activity of TiO₂ in solid-state photoreactions. Discoloration of famotidine in the presence of TiO₂ could be explained by several photocatalytic reaction models. Thus, the key factors in the reaction related to discoloration of the famotidine were the generation of radicals, as described earlier. On irradiation, e⁻ and h⁺ are produced over the surface of TiO₂. However, the major cause of the reaction is thought to have been ·OH and/or HO₂· because these are more mobile. Thus, e⁻ and h⁺ were continuously generated during the period of irradiation, but the probability of the production of ·OH and/or HO₂· depended on RH because RH determines the availability of the water molecules that are needed to generate ·OH and/or HO₂·. The reason the photocatalytic activity of the anatase form was more remarkable than that of the rutile form may be the ability to convert water molecule to radicals under low moisture conditions.

The main result of this study indicates that TiO₂ may decrease the photostability of drug because of its photocatalytic activity. The rutile form was shown to be preferable to the anatase form in improving the photostability of famotidine. In conclusion, to use TiO₂ as a pharmaceutical excipient, the photocatalytic activity of TiO₂ needs to be determined first. Furthermore, mutual interactions between TiO₂ and drugs need to be investigated in the preformulation stage.

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