Evaluation of Titanium Dioxide as a Pharmaceutical Excipient for Preformulation of a Photo-Labile Drug: Effect of Physicochemical Properties on the Photostability of Solid-State Nisoldipine

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To characterize the photocatalytic activity of TiO_2 *via* solid-state reaction, the relationship between the physicochemical properties and photocatalytic activity of TiO_2 was investigated and estimated from the results of photodegradation of nisoldipine. The photodegradation of nisoldipine was significantly enhanced by addition of TiO_2. Two degradation products, nitroso-phenylpyridine derivative and nitro-phenylpyridine derivative, were formed. The degree of photocatalytic activity of TiO_2 was quite different between the various types of TiO_2 investigated, even when the crystalline phase was the same. As a result of the investigations into the relationship between the photocatalytic activity and physicochemical properties of TiO_2, it was found that for the rutile form the photocatalytic activity has good correlation with specific surface area of TiO_2, but poor correlation with water loss on drying of TiO_2. However, for the anatase form, the photocatalytic activity has good correlation with water loss on drying of TiO_2, but poor correlation with specific surface area. Moreover, it was found that the crystallinity of TiO_2 has a moderate correlation with the photocatalytic activity of both crystal forms of TiO_2. These results suggest that a degree of photocatalytic activity of TiO_2 depends on the various physicochemical properties of each type of TiO_2 investigated.

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

Recently, many studies have been performed on titanium dioxide (TiO_2), which is known as a strong photocatalyst.[1—4] It is one type of inorganic pigment used in a wide range of industrial fields. It has also been used for solid pharmaceutical products as a coating material and its purity has been strictly regulated. According to Japanese Pharmacopoeia XIV, more than 98.5% purity is required, and more than 99.0% purity is required according to United States Pharmacopeia XXV. In our previous study, it was clarified that famotidine, which is stable against light, was easily degraded and discolored with the addition of TiO_2.[5] Therefore, a preformulation study is essential to thoroughly clarify the effect of TiO_2 addition on drug decomposition, in order to maintain the high quality of pharmaceutical products containing this excipient.

The photocatalytic activity of TiO_2 has not been defined directly and is estimated by either the degree of discoloration or degradation of photolabile compounds. In this study, nisoldipine (isobutylmethyl-1,4-dihydro-2,6-dimethyl-4-(2′-nitrophenyl)-pyridine-3,5-dicarboxylate, NS), known as an excellent calcium channel blocker, was used as a target compound and the effect of TiO_2 addition on the photodegradation of this drug was examined with regard to the photocatalytic activity of TiO_2. The relationship between the physiochemical properties of TiO_2 and the degree of photocatalytic activity of TiO_2 was also investigated.

Experimental

Materials Ten types of commercially available TiO_2 were used. Six of these were of the anatase form and the remainder was the rutile form. Anatase forms were obtained from Teika Co., Ltd. (A-1, A-5, A-6), Nacalai Tesque Inc. (A-2), Toho Titanium Co., Ltd. (A-3) and Freund Corporation (A-4). Rutile forms were obtained from Teika Co., Ltd. (R-1, R-4), Showa Chemical Co., Ltd. (R-2) and Toho Titanium Co., Ltd. (R-3). In order to strictly examine the effect of TiO_2 on photodegradation of NS, these samples were not surface coated with any material. NS was obtained from Permachem Asia, Ltd. All other chemicals and reagents were analytical grade.

Photodegradation Test The samples used for the photodegradation test were prepared as follows. NS was dissolved in methanol (1 mg/ml) and 50 μl of the solution was added onto 10 mg of each sample of TiO_2 powder. After thorough dispersion, the suspension was dried under vacuum.

Each sample was irradiated with a D65 lamp (illuminance: 3500 lx) at 25 °C in a light-irradiation tester (LIGHTTRON LT-120, Nagano Science, Japan). After the designated irradiation times, the amount of NS remaining in the sample was determined by HPLC. The average of three determinations was plotted as % NS remaining.

High-Performance Liquid Chromatography (HPLC) Analysis NS was analyzed using an HPLC system consisting of a solvent delivery system and an UV detector (LC-10Avp system, Shimadzu, Japan) at a detection wavelength of 235 nm, or a photodiode array detector (Model 996, Waters) at wavelengths in the range of 220—360 nm. The prepacked column (Mightysil RP-18, 5 μm, 4.6×150 mm, Merck) was operated at 35 °C with a flow rate of 1.7 ml/min. The mobile phase consisted of methanol : water (63 : 37 volume ratio). After irradiation, each sample was dissolved in the internal standard solution (methanolic solution of diphenyl) and an aliquot of 50 μl was injected into the chromatograph.

The amount of photodegradation products of NS, nitroso-pyridine derivative (isobutylmethyl-2,6-dimethyl-4-(2′-nitrosophenyl)-pyridine-3,5-dicarboxylate, NTS) and nitro-pyridine derivative (isobutylmethyl-2,6-dimethyl-4-(2′-nitrophenyl)-pyridine-3,5-dicarboxylate, NTR), was calculated from the ratio of specific extinction reported in previous literature.[6]

Characterization of TiO_2 Particles Specific surface areas of TiO_2 powders were determined using nitrogen gas adsorption apparatus (Flowsorb II model 2300, Shimadzu, Japan) at liquid nitrogen temperature.

FT-IR spectra were obtained by a powder-diffuse reflectance method on a Fourier Transform-infrared spectrophotometer (Spectrum One, PerkinElmer Japan) with analysis of the TiO_2 powder dispersed in KBr powder (sample concentration 5 w/w%).

Water loss on drying of TiO_2 was measured by a thermogravimetric method (Thermo Plus TG8120, Rigaku Denki, Japan), using approximately 7 mg samples in aluminum pans at a constant scanning speed of 10 °C/min between 35 and 100 °C, under a nitrogen gas flow (100 ml/min).

Relative crystallinity was determined using powder X-ray diffraction[7] (RINT Ultima, Rigaku Denki, Japan) with nickel-filtered Cu*K*α radiation

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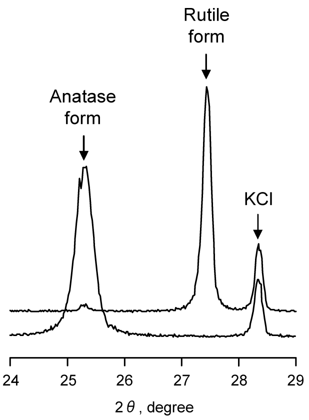

Fig. 1. Powder X-Ray Diffraction Patterns for the Anatase (A-5) and Rutile Forms (R-4) of TiO_2 and KCl

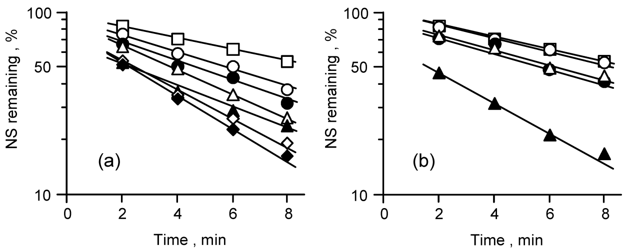

Fig. 2. The Effect of Various Types of TiO_2 Powders on the Photodegradation of NS under Irradiation with a D65 Lamp

(a) Anatase form; (○) A-1, (●) A-2, (△) A-3, (▲) A-4, (◇) A-5, (◆) A-6, (□) NS only, and (b) rutile form; (○) R-1, (●) R-2, (△) R-3, (▲) R-4, (□) NS only.

(30 kV, 30 mA) in the 2θ range from 20 to 80°. The scan speed was 4°/min and the scan time constant was 1 s. Relative crystallinity was calculated by the area ratio of peaks attributable to either anatase ($2\theta=25.4°$) or rutile ($2\theta=27.4°$) to that of KCl powder ($2\theta=28.4°$), which was used as an internal standard (Fig. 1).

Results

Photocatalytic Activity of TiO_2 Figure 2 shows the effect of the various types of TiO_2 powders on the time course of photodegradation of NS. NS without TiO_2 was rapidly degraded and the percentage of NS remaining decreased to 53% after 8 min irradiation. With addition of TiO_2 to NS, the photodegradation process was significantly accelerated, but the degree of photodegradation acceleration was quite different among the different types of TiO_2. In Fig. 2, R-1 did not show any remarkable effect on the photodegradation of NS, whereas A-6 and R-4 exhibited a remarkable acceleration effect to photodegradation, and the percentage of NS remaining decreased to only 16% after 8 min irradiation. These photodegradation processes apparently followed a first order reaction. Thus, Table 1 shows the apparent photodegradation rate constants of NS for the various types of TiO_2. It is evident that the photocatalytic activity of TiO_2 was quite different among the various types of TiO_2, even if the crystalline phase was the same. In particular, R-4 showed a higher photocatalytic activity than any of the anatase forms, except for A-6. However, the other three types of rutile form displayed lower photocatalytic activity than those of anatase forms.

Table 1. Apparent Photodegradation Rate Constants for Various Types of TiO_2

k, min^{-1}			
Anatase form		Rutile form	
A-1	0.117	R-1	0.073
A-2	0.136	R-2	0.108
A-3	0.203	R-3	0.103
A-4	0.162	R-4	0.220
A-5	0.172		
A-6	0.221		

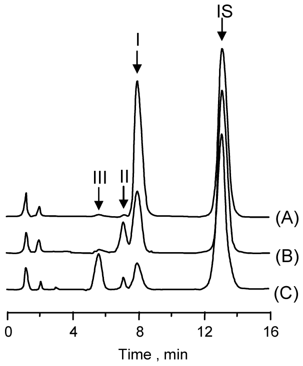

Fig. 3. HPLC Chromatograms for (A) NS, (B) NS after 8 min Irradiation with a D65 Lamp and (C) NS with TiO_2 (A-6) after 8 min Irradiation with a D65 Lamp

Each peak was assigned as (I) NS, (II) NTS and (III) NTR, respectively.

Table 2. Characteristics of NS and Photodegradation Products

Peak No.	Compound	Relative retention time to IS	Maximum absorption wavelengths, nm
I	Nisoldipine (NS)	0.60	239, 339
II	Nitroso-pyridine derivative (NTS)	0.54	281, 315
III	Nitro-pyridine derivative (NTR)	0.42	272

IS: internal standard.

Figure 3 shows the HPLC chromatograms of samples obtained after 8 min irradiation. There were two peaks excepting NS (I) and internal standard (IS) at the same relative retention time in the three chromatograms, (A), (B), (C). The maximum absorption wavelengths for each peak are shown in Table 2. These maximum absorption wavelengths were compared to the results reported in previous literature.[6] So, peaks II and III were identified as those of NTS and NTR, respectively. Photodegradation of NS without TiO_2 resulted in mainly NTS as a direct photooxidation product. On the contrary, NS concurrently formed two kinds of photodegradation products, NTS and NTR, with the addition of TiO_2. In particular, after the addition of A-6 to NS, the degree of NTR formation significantly increased compared with that of NTS formation (Fig. 4). This fact suggests that NTR is a degradation product derived from photocatalytic oxidation. The formation ratio of NTR to NTS for each sample after 8 min irradiation is summarized in Table 3. Figure 5 shows the relationship between the formation ratio of NTR to NTS and the apparent degradation rate constant of NS. Good correlation was established between the product formation ratio and degradation rate constant for all of these crystal forms ($r=0.971$, $p<0.05$ for anatase, $n=6$ and $r=0.977$, $p<0.05$ for rutile form, $n=4$). Therefore, the formation ratio of NTR to NTS is defined hereafter as the index of photocatalytic activity of TiO_2.

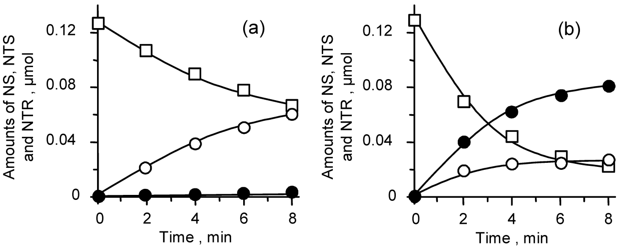

Fig. 4. Effect of TiO_2 (A-6) on the Photodegradation Time-Courses of NS and Formation of Photodegradation Product

(a) NS only; (b) NS with TiO_2. Key: (□) NS; (○) NTS; (●) NTR.

Table 3. Formation Ratio of NTR to NTS for Various Types of TiO_2 after 8 min Irradiation

Formation ratio of NTR to NTS			
Anatase form		Rutile form	
A-1	0.172	R-1	0.255
A-2	0.306	R-2	0.638
A-3	2.47	R-3	1.08
A-4	1.11	R-4	2.59
A-5	0.961		
A-6	2.95		

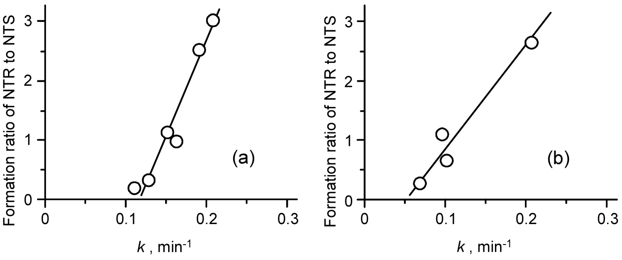

Fig. 5. Relationship between the Apparent Photodegradation Rate Constant, *k* and the Formation Ratio of NTR to NTS

(a) Anatase form; (b) rutile form.

Table 4. Specific Surface Area of Various Types of TiO_2

Specific surface area, m²/g			
Anatase form		Rutile form	
A-1	8.19	R-1	5.38
A-2	14.9	R-2	13.8
A-3	22.7	R-3	17.6
A-4	23.6	R-4	78.2
A-5	44.2		
A-6	117.6		

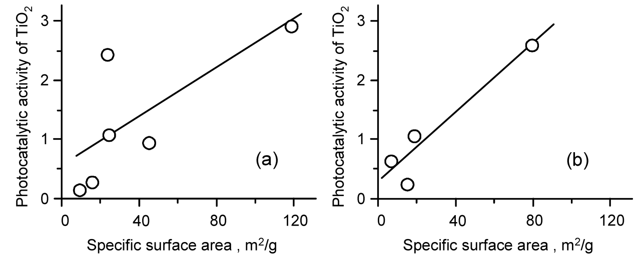

Fig. 6. Relationship between Specific Surface Area and Photocatalytic Activity of TiO_2

(a) Anatase form; (b) rutile form.

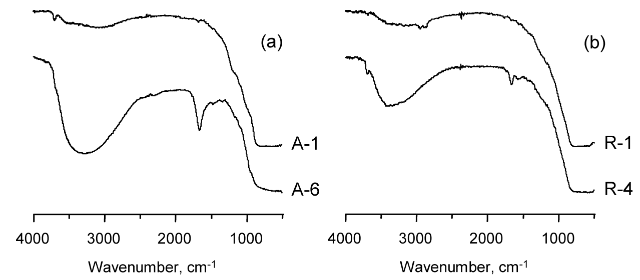

Fig. 7. Absorption Peaks in the FT-IR Spectra of TiO_2 Powders

(a) Anatase form; (b) rutile form.

Characterization for Photocatalytic Activity of TiO_2 The specific surface area of TiO_2 has been generally considered as a controlling factor of the photocatalytic activity: the light exposure area and number of reaction sites on the surface of TiO_2 powder would necessarily increase with an increase in specific surface area. Table 4 shows the specific surface area of the various types of TiO_2 investigated. For the anatase form, the smallest specific surface area was 8.19 m^2/g (A-1) and the largest was 117.6 m^2/g (A-6). For the rutile form, the smallest specific surface area was 5.38 m^2/g (R-1) and the largest was 78.2 m^2/g (R-4), indicating that the specific surface area was quite different even though the crystal phase was the same. Figure 6 shows the relationship between the specific surface area of various types of TiO_2 and their photocatalytic activity. For the both crystal forms, good correlations were observed between them. Particularly, a correlation for the rutile form ($r=0.951$, $n=4$) was better than that for the anatase form ($r=0.738$, $n=6$).

The amount of binding water associated with TiO_2 has also been considered as a contributing factor to photocatalytic activity, because our previous study[5] confirmed that relative humidity remarkably affects photocatalytic activity of TiO_2, and that water molecules in the atmosphere have an important role in the photocatalytic activity of TiO_2. Figure 7 shows the FT-IR spectra of TiO_2. From these results, the broad absorption peak in the wavenumber range from 2500 to 3900 cm^{-1} and the peak at 1600 cm^{-1} were appreciably different among the samples of TiO_2. These absorption peaks are closely related with stretching vibrations of the hydroxyl functional group.[11] Thus, to clarify the effect of water adsorption, the loss of water on drying of TiO_2 was measured. Table 5 shows water loss on drying for various types of TiO_2 powder, and Fig. 8 shows the relationship between the water loss and photocatalytic activity. Contrary to the results in Fig. 6, a relatively strong correlation was observed for the anatase form ($r=0.712$, $n=6$), whereas a very poor correlation was seen for the rutile form ($r=0.498$, $n=4$).

Finally, the relationship between the photocatalytic activity and crystallinity of TiO_2 was investigated. The difference in the crystal structure has been generally recognized as a factor closely related to the difference in photocatalytic activity between the anatase and rutile forms. The relative crystallinity of the various types of TiO_2 is summarized in Table 6, and the relationship between the relative crystallinity and photocat-

Table 5. Water Loss on Drying for Various Types of TiO_2

Water loss on drying, %			
Anatase form		Rutile form	
A-1	0.12	R-1	0.10
A-2	0.15	R-2	0.07
A-3	0.31	R-3	0.11
A-4	0.22	R-4	0.11
A-5	0.71		
A-6	6.48		

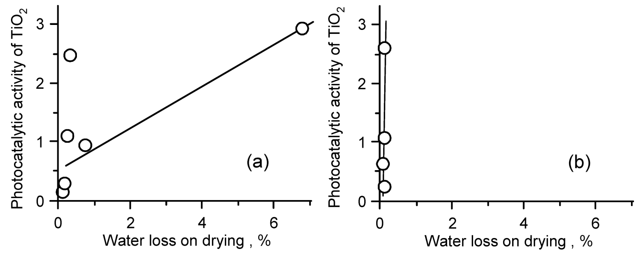

Fig. 8. Relationship between the Water Loss on Drying and Photocatalytic Activity of TiO_2

(a) Anatase form; (b) rutile form.

Table 6. Relative Crystallinity of Various Types of TiO_2

Relative crystallinity			
Anatase form		Rutile form	
A-1	5.97	R-1	4.65
A-2	6.79	R-2	4.72
A-3	3.37	R-3	3.70
A-4	5.56	R-4	3.34
A-5	2.99		
A-6	1.83		

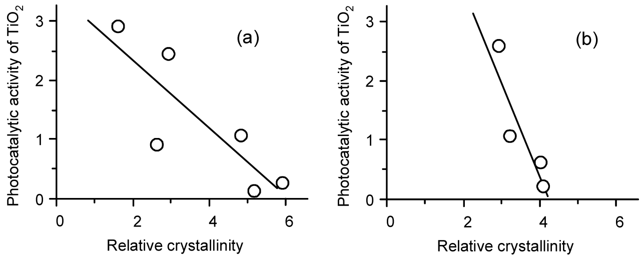

Fig. 9. Relationship between Relative Crystallinity and Photocatalytic Activity of TiO_2

(a) Anatase form; (b) rutile form.

alytic activity is shown in Fig. 9. A good correlation was established between these for all of the crystal forms ($r=0.837$ for anatase, $n=6$ and $r=0.898$ for rutile form, $n=4$).

Discussion

The photodegradation of NS by light irradiation was more or less enhanced by addition of TiO_2, and the difference in the degree of photodegradation was caused by the difference of photocatalytic activity. Particularly, for the rutile form, R-1 had little effect on the degradation of NS. On the other hand, R-4 showed a high photodegradation effect as did A-6, which exhibited higher photocatalytic activity than that of any other anatase form measured. These facts suggest that the photocatalytic activity depends not only on the crystal form, but also on the other physicochemical properties of each type of TiO_2.

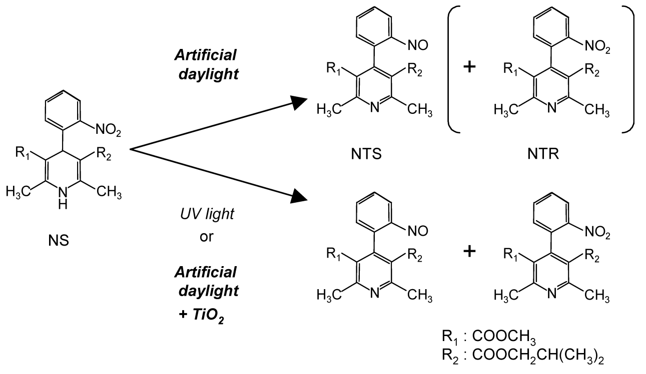

Fig. 10. Possible Photodegradation Processes of NS

In the photodegradation processes, two kinds of photodegradation products, NTS and NTR, have been detected. It has been reported that NTS was a direct photooxidation product of NS under irradiation with artificial daylight or white fluorescent light,[8,9] whereas NTR is predominantly formed under UV light irradiation.[9,10] Therefore, in the presence of TiO_2, NTR would be produced even if the light source has low irradiation energy (Fig. 10). In addition, as the formation ratio of NTR to NTS becomes larger with increasing photocatalytic activity, it can be said that NTR is a photocatalytic degradation product with TiO_2 present and after irradiation.

According to the results described above, it is clear that the photocatalytic activity of TiO_2 is dependent not only on the crystal form, but also on the micromeritic properties of TiO_2 powders. Therefore, the relationship between the photocatalytic activity of TiO_2 and the physiochemical properties of TiO_2 was investigated.

For anatase form, photocatalytic activity was correlated with both specific surface area and water loss on drying. Therefore, for the anatase form, changes in specific surface area and water loss on drying affect the photocatalytic activity of TiO_2. On the other hand, photocatalytic activity of the rutile form was quite well correlated with specific surface area, but not correlated with water loss from drying. The rutile form has little water adsorption, because the values of water loss on drying were very small. Therefore, for the rutile form, a change in the specific surface area dramatically affects the photocatalytic activity of TiO_2.

Additionally, it was clear that for both crystal forms an increase of relative crystallinity of TiO_2 led to a decrease of photocatalytic activity; the slope of the regression line for the rutile form was steeper than that for the anatase form (Fig. 9). This fact suggests that the relative crystallinity of the rutile form is more sensitive for photocatalytic activity.

According to these facts, it might be possible to predict the photocatalytic activity of TiO_2, particularly for the rutile form, by measuring the specific surface area of TiO_2. Previously, we discussed that the photocatalytic activity of TiO_2 can comprise the high quality and chemical integrity of pharmaceutical products. However, TiO_2 is an essential excipient, because of its whiteness and light-proofing ability. Therefore the information on the relationship between photocatalytic activity and physicochemical properties of TiO_2 will be useful to make a rational selection of the appropriate type and grade of commercial TiO_2 for this use.

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