

# Iron Oxides in Titanium Dioxide-Free Coatings Protect Photolabile Active Pharmaceutical Ingredients in Oral Solid Dosage Forms

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## Introduction

### Titanium Dioxide (TiO<sub>2</sub>, E171)

In medicines, TiO<sub>2</sub> is often included in tablet coatings and capsule shells for the following effects 1,2:

Act as a pigment and opacifier

Provide protection from UV-radiation

Enable consistent product appearance

### E171 Ban in European Union (EU)

In 2022, the EU Commission banned TiO<sub>2</sub> in foods due to lack of evidence oral digestion of TiO<sub>2</sub> is safe.

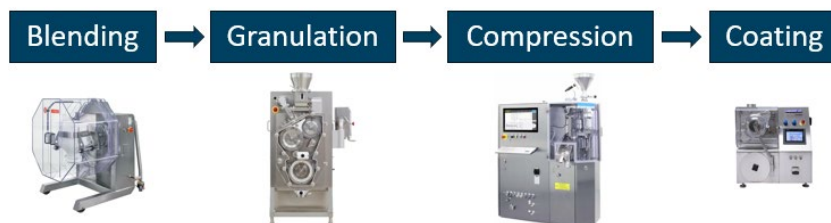
By February 2025, the EU will make a decision on whether to ban the use of TiO<sub>2</sub> in medicines, but highly suggested industry begin searching for alternatives.

## Objectives

Evaluate the levels of iron oxide (FeO) necessary to protect photolabile active pharmaceutical ingredients (APIs) in tablets coated with titanium dioxide-free (TF) coatings.

## Methods

Figure 1. Schematic of preparing and coating tablets.



- Photolabile API was blended with standard pharmaceutical excipients and compressed into 500 mg tablets.
- Tablets were coated to 4% weight gain (WG) using an O'Hara Labcoat benchtop coater with PVA-based TF coatings provided by Colorcon, and with TiO<sub>2</sub> reference coatings.
- Slack-variable mixture model DOE was set up in Fusion and JMP with the maximum total iron oxide concentration fixed at 1.5%.
- Coated tablets were tested in an Ametek Atlas Suntest CPS+ photochamber following ICH Q1B guidelines.
- Photodegradation was quantified by UPLC using a commercial stability indicating method.

**Table 1. Slack-variable mixture model design.**

Run	Red FeO	Yellow FeO	Black FeO	CaCO <sub>3</sub>
1	0	0.50	0	34.50
2	0.62	0.62	0.25	33.51
3	1	0	0.50	33.50
4	0	1	0	34.00
5	0.50	1	0	33.50
6	0.22	0.22	0.34	34.22
7	0.50	0.50	0.50	33.50
8	0	0	0.25	34.75
9	0	1	0.50	33.50
10	1	0	0.50	33.50
11	0	1	0.50	33.50
12	0.44	0.44	0.19	33.93
13	1	0	0	34.00
14	0.72	0.22	0.34	33.72
15	0.22	0.72	0.34	33.72
16	1	0.50	0	33.50
17	0	0	0.50	34.50
18	0	0	0.50	34.50
19	0	0	0.00	35.00
20	0.44	0.44	0.19	33.93
21	0.50	0	0	34.50

## Results

DOE Analysis and Response Surface Plots

**Table 2. Statistically significant ( $p < 0.05$ ) model coefficients.**

Coded Name	Coefficient Value	Coefficient Standard Error	Coefficient t Statistic	P-Value
Constant	0.200	---	---	---
Red FeO	-0.033	0.007	-4.9913	<b>0.0002</b>
Yellow FeO	-0.030	0.007	-4.5013	<b>0.0005</b>
(Red FeO) <sup>2</sup>	0.027	0.009	2.8912	<b>0.0118</b>
(Yellow FeO) <sup>2</sup>	0.038	0.009	4.1521	<b>0.0010</b>
(Black FeO) <sup>2</sup>	-0.022	0.009	-2.3565	<b>0.0335</b>
Red*Yellow	0.041	0.007	5.5973	<b>0.0001</b>

Figure 2. Control groups. There is photodegradant present in tablet cores from API manufacturing and tablet compression.

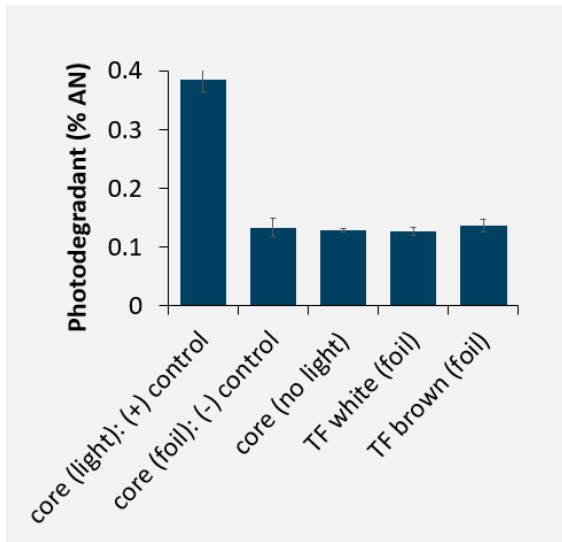


Figure 3. TF coatings with only Red FeO up to 8% w/w with corresponding tablet images.

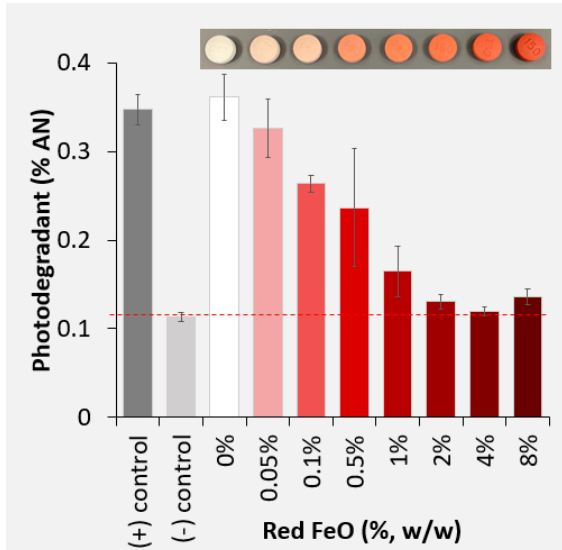


Table 3. Photodegradant ranked from lowest to highest levels formed.



















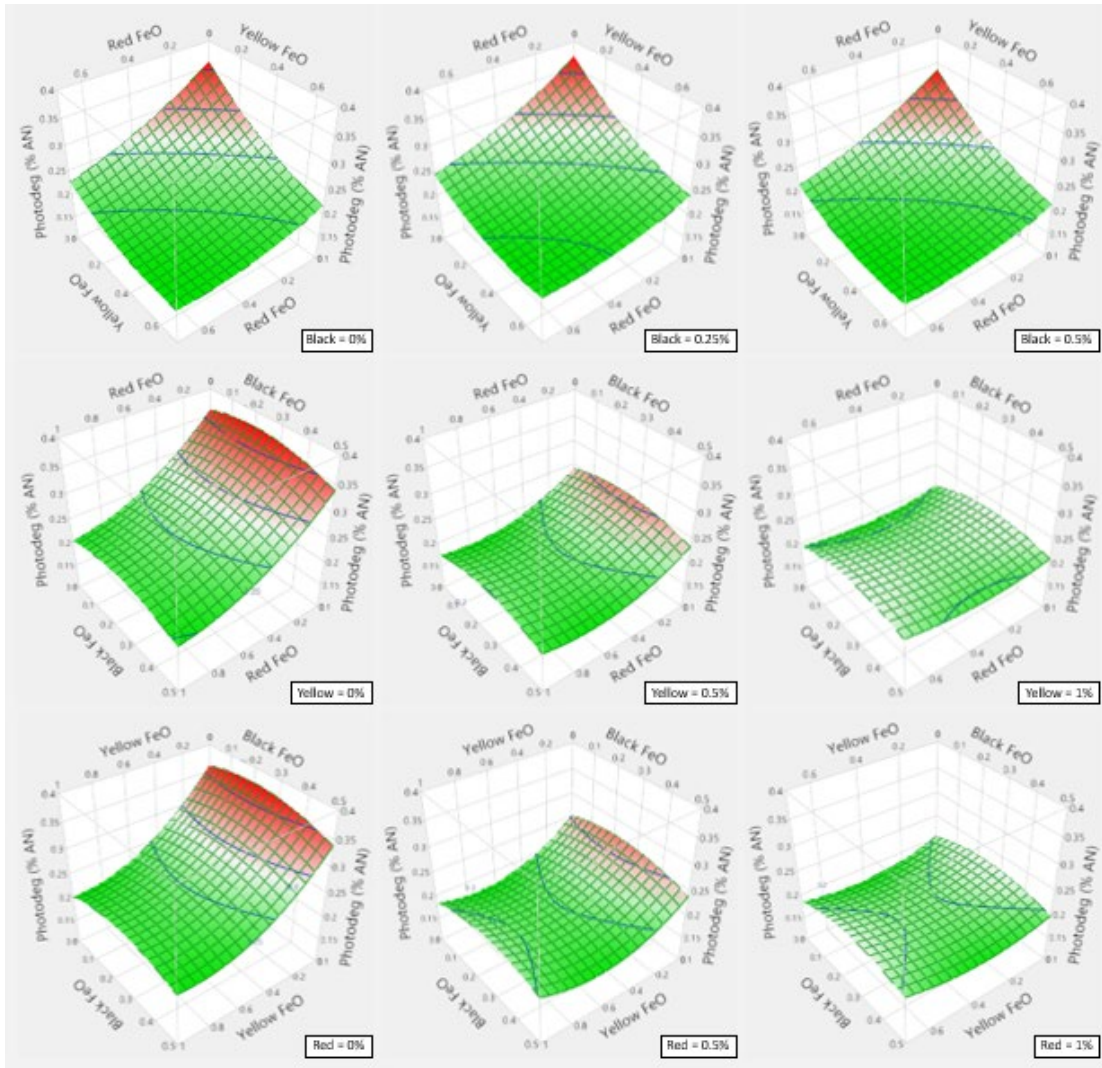
	%AN	Red	Yel	Bla
	0.172	1	0.50	0
	0.180	0.62	0.62	0.25
	0.184	0.50	0.50	0.50
	0.184	1	0	0.50
	0.190	0.50	1	0
	0.190	0.72	0.22	0.34
	0.197	0	1	0
	0.203	0	1	0.50
	0.208	0.44	0.44	0.19
	0.208	1	0	0
	0.222	0.22	0.72	0.34
	0.242	0.22	0.22	0.34
	0.243	0	0.50	0
	0.252	0.50	0	0
	0.280	<b>TiO<sub>2</sub> standard</b>		
	0.337	0	0	0.50
	0.355	0	0	0
	0.387	0	0	0.25

Figure 4. Response surface plots of formed photodegradant (% AN) with respect to FeO concentration. Each plot displays the relationship between two iron oxides with the third iron oxide black, yellow or red at a fixed concentration shown at the right bottom corner.



### Absorbance and Transmittance Spectra of Coating Suspensions

Figure 5. Transmittance and absorbance from 200 to 800 nm of TiO<sub>2</sub> and TF coatings containing only one type of iron oxide.

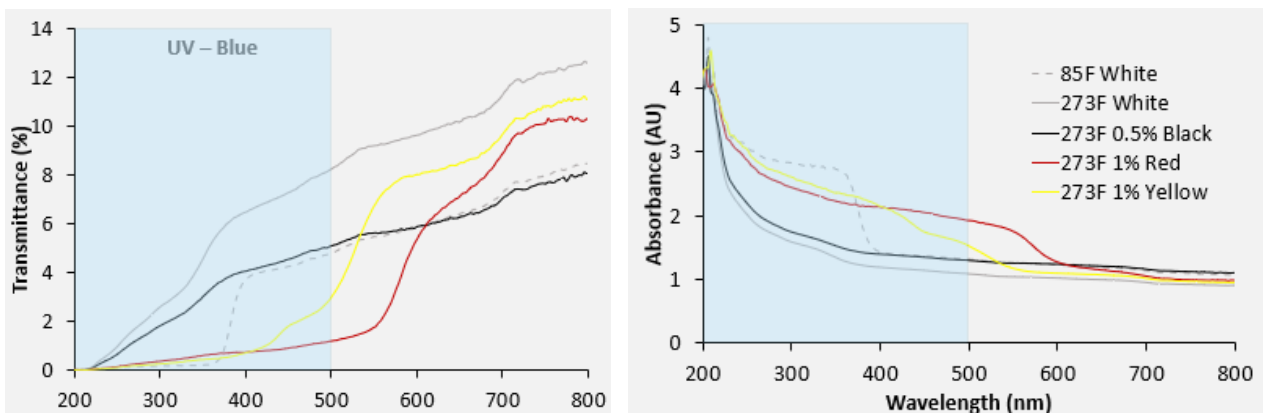
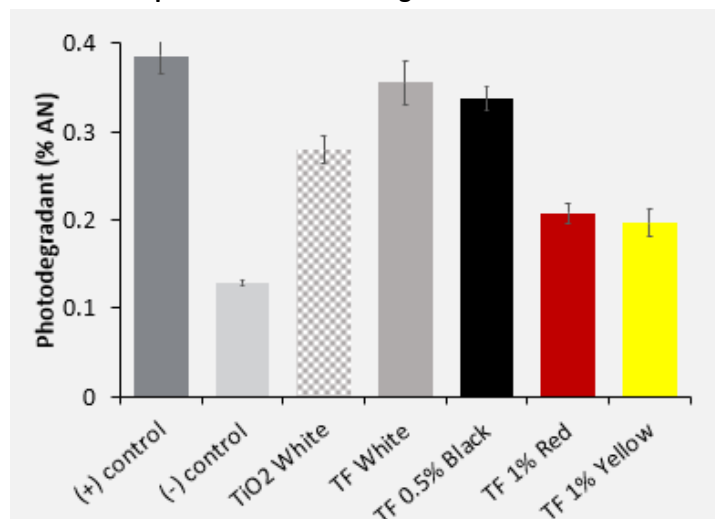


Figure 6. Photodegradant measured in TiO<sub>2</sub>- and TF-coated tablets with one type of iron oxide whose transmittance and absorbance spectra are shown in Figure 5.



## Conclusions

- TF coatings containing  $\geq 1\%$  red or yellow FeO offered high levels of photoprotection, while black iron oxide had no effect. The TiO<sub>2</sub> standard had similar photodegradation to TF coatings with only 0.5% red or yellow.
- It is known that most photosensitive APIs degrade in UV-Blue light; when red or yellow iron oxide is present in this PVA-based TF coating, there is low transmittance in the UV-Blue wavelength range.
- Follow up experiments include studying the photoprotective impact of FeO in different polymer-based TF coatings and verifying the DOE results with other photolabile APIs.

## References

1. Blundell R, Butterworth P, Charlier A, et al. The Role of Titanium Dioxide (E171) and the Requirements for Replacement Materials in Oral Solid Dosage Forms: An IQ Consortium Working Group Review. *Journal of Pharmaceutical Sciences* 2022;111(11):2943-2954. <https://doi.org/https://doi.org/10.1016/j.xphs.2022.08.011>.
2. Hancock B, Harris D, Kaye J, et al. Titanium Dioxide (E171 Grade) and the Search for Replacement Opacifiers and Colorants: Supplier Readiness Survey, Case Studies and Regulatory Perspective. *Journal of Pharmaceutical Sciences* 2024;113(5):1285-1298. <https://doi.org/https://doi.org/10.1016/j.xphs.2023.12.006>.

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