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

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Introduction

Titanium Dioxide (TiO2, E171)

In medicines, TiO2 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)

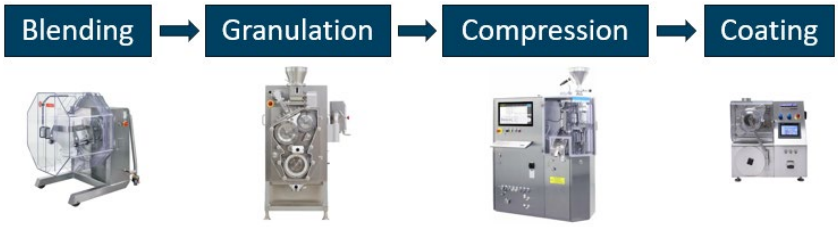
In 2022, the EU Commission banned TiO2 in foods due to lack of evidence oral digestion of TiO2 is safe.
By February 2025, the EU will make a decision on whether to ban the use of TiO2 in medicines, but highly suggested industry begin searching for alternatives.

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_2 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	$CaCO_3$
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	**0.0002**
Yellow FeO	-0.030	0.007	-4.5013	**0.0005**
$(Red\ FeO)^2$	0.027	0.009	2.8912	**0.0118**
$(Yellow\ FeO)^2$	0.038	0.009	4.1521	**0.0010**
$(Black\ FeO)^2$	-0.022	0.009	-2.3565	**0.0335**
Red*Yellow	0.041	0.007	5.5973	**0.0001**

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

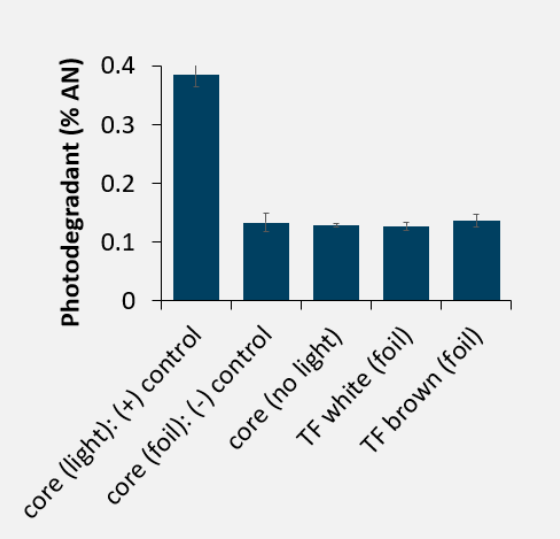


Figure 3. TF coatings with only Red FeO up to 8% w/w with corresponding tablet images.

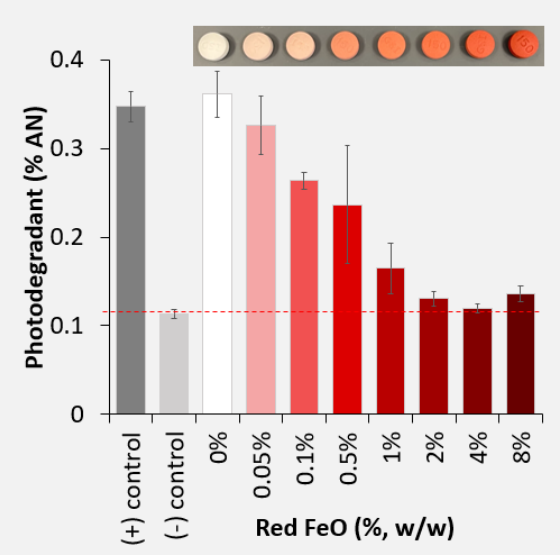
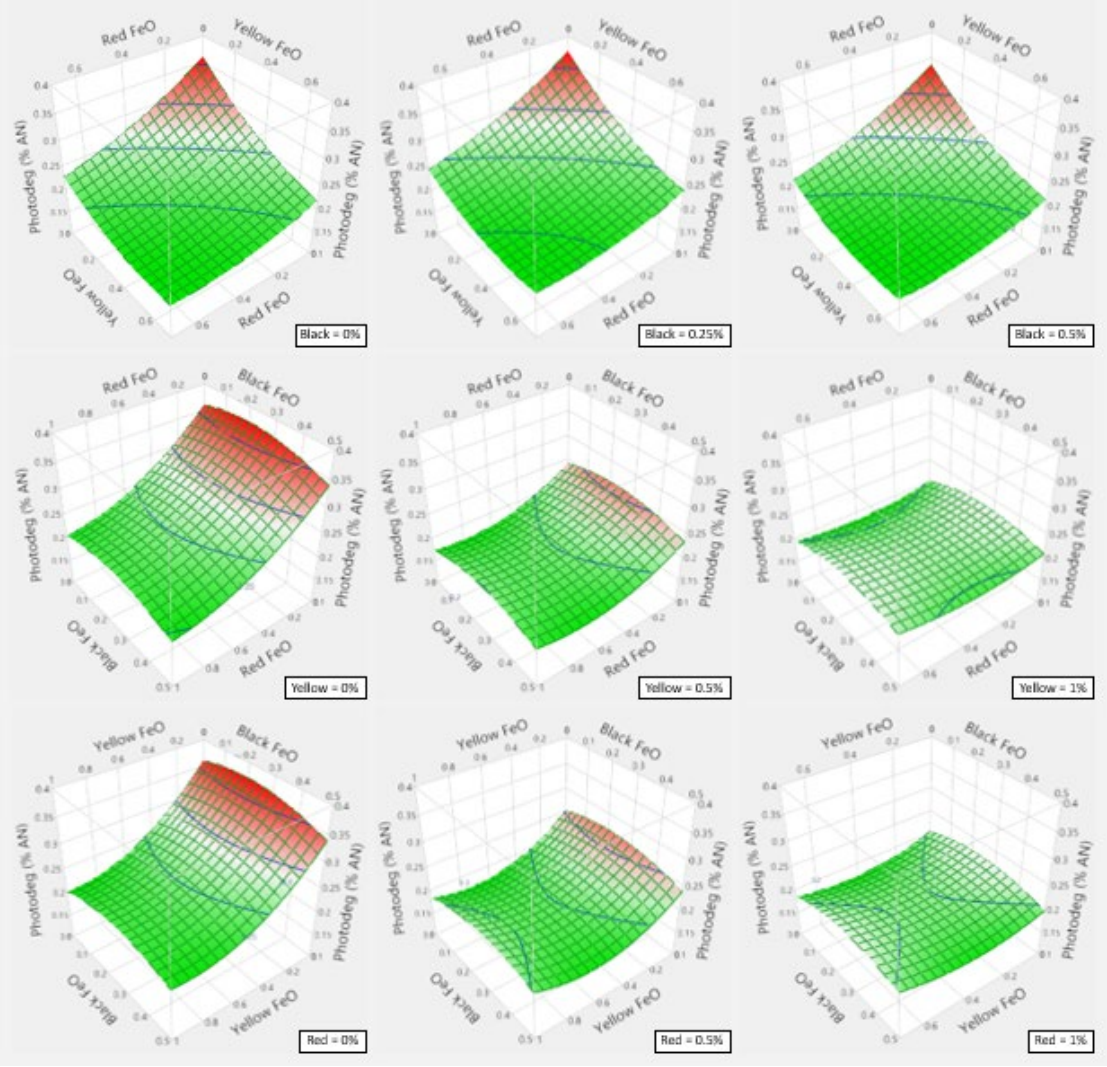


Table 3. Photodegradant ranked from lowest to highest levels formed.

	%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	TiO_2 standard		
	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 TiO2 and TF coatings containing only one type of iron oxide.

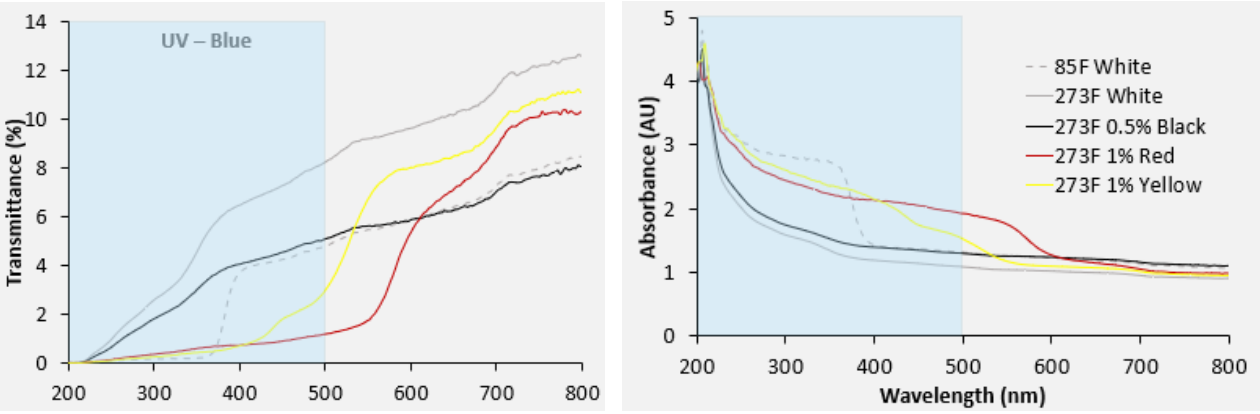
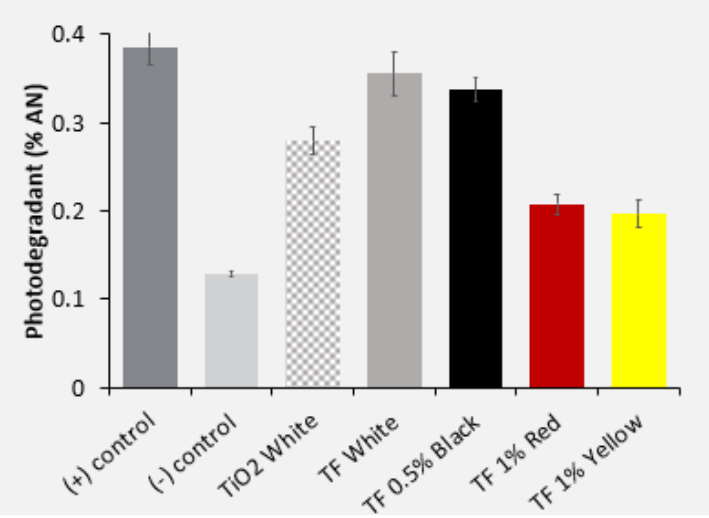


Figure 6. Photodegradant measured in TiO2- and TF-coated tablets with one type of iron oxide whose transmittance and absorbance spectra are shown in Figure 5.



Conclusions

- TF coatings containing ≥1% red or yellow FeO offered high levels of photoprotection, while black iron oxide had no effect. The TiO_2 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.